=> s human cytomegalovirus immediate early
5360956 HUMAN
13915 CYTOMEGALOVIRUS
45642 IMMEDIATE
255417 EARLY
L1 74 HUMAN CYTOMEGALOVIRUS IMMEDIATE EARLY
(HUMAN(W)CYTOMEGALOVIRUS(W)IMMEDIATE(W)EARLY)
=> sort
ENTER (L1), L#, OR L# RANGE:l1
SORT ENTIRE ANSWER SET? (Y)/N:y
ENTER SORT FIELDS AND SORT DIRECTION (?):py
PROCESSING COMPLETED FOR L1
L2 74 SORT L1 PY

=> d ti 1-10

L2 ANSWER 1 OF 74 MEDLINE
TI Comparison of occurrence of antibodies to human cytomegalovirus as demonstrated by immunofluorescence and indirect hemagglutination techniques.

L2 ANSWER 2 OF 74 MEDLINE
TI Multiple spliced and unspliced transcripts from ***human*** ***cytomegalovirus*** ***immediate*** - ***early*** region 2 and evidence for a common initiation site within immediate-early region 1.

L2 ANSWER 3 OF 74 MEDLINE
TI Establishment of a rat cell line inducible for the expression of ***human*** ***cytomegalovirus*** ***immediate*** - ***early*** gene products by protein synthesis inhibition.
L2 ANSWER 4 OF 74 MEDLINE
TI Growth hormone gene expression in myoepithelial cells directed by various eucaryotic transcriptional regulatory sequences.
L2 ANSWER 5 OF 74 MEDLINE
TI Participation of two ***human*** ***cytomegalovirus*** ***immediate*** ***early*** gene regions in transcriptional activation of adenovirus promoters.

L2 ANSWER 6 OF 74 MEDLINE
TI Resistance to methylation de novo of the ***human*** ***cytomegalovirus*** ***immediate*** ***early*** enhancer in a model for virus latency and reactivation in vitro.
L2 ANSWER 7 OF 74 MEDLINE
TI Identification and characterization of the ***human*** ***cytomegalovirus*** ***immediate*** - ***early*** region 2 gene that stimulates gene expression from an inducible promoter.
L2 ANSWER 8 OF 74 MEDLINE
TI The use of biotinylated monoclonal antibodies and streptavidin affinity chromatography to isolate herpesvirus hydrophobic proteins or glycoproteins.

L2 ANSWER 9 OF 74 MEDLINE
TI Binding of transcription factors and creation of a large nucleoprotein complex on the human cytomegalovirus enhancer.
L2 ANSWER 10 OF 74 MEDLINE
TI The ***human*** ***cytomegalovirus*** ***immediate*** ***early*** gene promoter is a

strong promoter in cultured Drosophila melanogaster cells.

=> d 10 au,ti,so,ab

L2 ANSWER 10 OF 74 MEDLINE
AU Sinclair J H
TI The ***human*** ***cytomegalovirus*** ***immediate*** ***early*** gene promoter is a strong promoter in cultured Drosophila melanogaster cells.
SO Nucleic Acids Res, (1987 Mar 11) 15 (5) 2392.
Journal code: O8L. ISSN: 0305-1048.

=> s human cytomegalovirus
5360956 HUMAN
13915 CYTOMEGALOVIRUS
L3 1859 HUMAN CYTOMEGALOVIRUS
(HUMAN(W)CYTOMEGALOVIRUS)

=> s 1e1 region
12 1E1
176781 REGION
L4 0 1E1 REGION
(1E1(W)REGION)

=> s (ie1 region) or region(5a)ie1
127 IE1
176781 REGION
2 IE1 REGION
(IE1(W)REGION)
176781 REGION
127 IE1
22 REGION(5A)IE1
L5 22 (IE1 REGION) OR REGION(5A)IE1

=> s l5 and l3
L6 15 L5 AND L3

=> d au,ti,so,ab 1-15

L6 ANSWER 1 OF 15 MEDLINE
AU Kondo K; Kaneshima H; Mocarski E S
TI ***Human*** ***cytomegalovirus*** latent infection of granulocyte-macrophage progenitors.
SO Proc Natl Acad Sci U S A, (1994 Dec 6) 91 (25) 11879-83. Journal code: PV3. ISSN: 0027-8424.
AB We have investigated the interaction of ***human*** ***cytomegalovirus*** (CMV) with cultured primary
granulocyte-macrophage progenitors, a suspected natural site of viral latency, and have established conditions for latent infection and reactivation in this cell population. Progenitor cells from human fetal liver or bone marrow maintained a CD14+, CD15+, CD33+ cell surface phenotype during propagation in suspension culture. Exposure to human CMV did not reduce growth or alter the phenotype of these cells during a 4-week culture period. Viral replication was not detectable in these cells, although viral DNA, as measured by PCR analysis, persisted in a high proportion of cultured cells in the absence of delayed early

(beta) gene expression. Viral gene expression was restricted such that only ***ie1*** ***region*** transcripts were detected by PCR analysis of cDNA, and these transcripts were estimated to be present in no less than 2-5% of latently infected cells. Most of these transcripts remained unspliced, a result that strikingly contrasts with the splicing pattern normally seen during viral replication in permissive cells. Latent virus reactivated after prolonged, 16- to 21-day cocultivation of infected granulocyte-macrophage progenitors with permissive cells, results that support a role for the myelomonocytic cell population as a biological reservoir of latent human CMV and suggest that these cells may be the source of CMV DNA PCR-positive monocytes found in the peripheral blood of healthy carriers.

L6 ANSWER 2 OF 15 MEDLINE

AU Jenkins D E; Martens C L; Mocarski E S

TI ***Human*** ***cytomegalovirus*** late protein encoded by ie2: a trans-activator as well as a repressor of gene expression. SO J Gen Virol, (1994 Sep) 75 ( Pt 9) 2337-48.

Journal code: I9B. ISSN: 0022-1317.

AB In order to study the function of ***human*** ***cytomegalovirus*** (HCMV) immediate early gene 2 (ie2) (UL122) gene products made at late times during infection, cDNA clones were isolated from an expression library made with 74 h post-infection mRNA. Based on screening of the library, 1% of transcripts in infected cells at this time were ie2 region-specific, and transcripts encoding gamma IE2(338aa), a 40K late gene product, were more abundant than those encoding IE2(579aa), an alpha gene product made throughout infection. As expected, the cDNA capable of directing the expression of gamma IE2(338aa) was derived from a contiguous genomic ***region*** within exon 5 of the ***ie1*** /ie2 ***region*** . The cDNA clones encoding gamma IE2(338aa) and IE2(579aa) were compared for their ability to trans-activate viral and cellular promoters and to repress expression from the ie1/ie2 promoter via the ie2 cis-repression signal. Unexpectedly, gamma IE2(338aa) trans-activated a variety of test promoters when cotransfected with the major alpha gene product, IE1(491aa). Promoters derived from the cellular beta-actin gene, the simian virus 40 early region and the human immunodeficiency virus were all responsive to gamma IE2(338aa) plus IE1(491aa), although several beta promoters derived from the HCMV genome were unresponsive. Thus, this abundant late product from the ie2 region may play a role in trans-activation in addition to its role as a repressor of alpha gene expression.

L6 ANSWER 3 OF 15 MEDLINE

AU Daiminger A; Schalasta G; Betzl D; Enders G

TI Detection of ***human*** ***cytomegalovirus*** in urine samples by cell culture, early antigen assay and polymerase chain reaction.

SO Infection, (1994 Jan-Feb) 22 (1) 24-8.

Journal code: GO8. ISSN: 0300-8126.

AB With the advent of effective therapy rapid, sensitive and reliable assays for diagnosis of ***human*** ***cytomegalovirus*** (HCMV) infections are required. In a total of 1,928 urine samples, detection of HCMV-immediate early antigen in a spin amplified microplate culture by a monoclonal antibody and immunoperoxidase staining (EA-assay) was compared with virus isolation in cell culture. Sensitivity of the EA assay was 85.5% and specificity was 99.5% compared with virus isolation. Overall agreement of both assays was 97.8%. In addition, in 235/1,928 urine samples amplification of HCMV-DNA was performed by means of polymerase chain reaction (PCR) using primers from the immediate early ( ***IE1*** ) gene ***region*** and 141/1,928 using primers from the late region (LA). The sensitivity of PCR compared with virus isolation was 67.8% for IE1 primers and 94.1% for LA primers (statistical significance: $p < 0.01$, Chi-square-test). Overall agreement between virus isolation and PCR was 88.5% for IE1-PCR and 84.4% for LA-PCR. Discordant results were more often found in adults with acute infection and immunocompromised patients than in infants.

L6 ANSWER 4 OF 15 MEDLINE

AU Wang J; Razzaque A

TI Mapping and DNA sequence analysis of the cytomegalovirus transforming domain III (mtrIII).
SO Virus Res, (1993 Dec) 30 (3) 221-38.
Journal code: X98. ISSN: 0168-1702.
AB The transforming activity of XbaI fragment E (map units 0.685-0.770) of ***human*** ***cytomegalovirus*** Towne strain was originally localized in two terminal segments, 3 kb XbaI-BamHI EM (mtrII) and 7.5 kb BamHI-XbaI EJ (mtrIII). Three immediate-early genes, IE1 to IE3, are located in the same region (map unit 0.685-0.770), and IE1 is located in the EJ fragment. IE1 protein increases chromatin transcriptional activity and causes alteration in chromatin conformation. In this study, we have investigated the potential transforming activity of ***IE1*** , ***IE1*** plus its promoter-regulatory ***region*** (IE P/R), and the remaining fragment of EJ after deletion of IE1 plus IE P/R. Our results clearly demonstrate that IE1 or IE1 plus IE P/R is not involved in transformation, and that the transforming activity of mtrIII is located in a 2.1 kb SalI-XbaI subfragment of EJ. DNA sequence analysis reveals four putative open reading frames (ORFs) L1, L2, L3 and R1 in the 2.1 kb fragment. The data from the deletion clones of the 2.1 kb fragment and also by disruption of individual ORFs by restriction enzyme digestion, suggest that a complete ORF L3 or R1 may be essential but not sufficient for the transforming activity. Because significant reduction in transforming activity is obtained by interrupting ORFs LI and L2, these ORFs may be required for the full transforming activity.

L6 ANSWER 5 OF 15 MEDLINE
AU Bryant L A; Sinclair J H
TI Inhibition of ***human*** ***cytomegalovirus*** major immediate early gene expression by antisense RNA expression vectors. SO J Gen Virol, (1993 Sep) 74 ( Pt 9) 1965-7.
Journal code: I9B. ISSN: 0022-1317.
AB We have used antisense oligonucleotides and expression vectors to inhibit ***human*** ***cytomegalovirus*** (HCMV) major immediate early (IE) gene expression. We find that oligonucleotides complementary to the HCMV 72K IE protein ( ***IE1*** ) coding ***region*** do inhibit HCMV infection, but this is non-specific. However, the use of certain antisense expression vectors, which express short oligonucleotides complementary to IE1, specifically inhibits IE1 expression at the protein level after introduction of IE expression vectors into cells or after HCMV infection.
L6 ANSWER 6 OF 15 MEDLINE
AU Pari G S; Kacica M A; Anders D G
TI Open reading frames UL44, IRS1/TRS1, and UL36-38 are required for transient complementation of ***human*** ***cytomegalovirus*** oriLyt-dependent DNA synthesis.
SO J Virol, (1993 May) 67 (5) 2575-82.
Journal code: KCV. ISSN: 0022-538X.
AB Previous results showed that plasmids containing ***human*** ***cytomegalovirus*** (HCMV) oriLyt are replicated after transfection into permissive cells if essential trans-acting factors are supplied by HCMV infection (D. G. Anders, M. A. Kacica, G. S. Pari, and S. M. Punturieri, J. Virol. 66:3373-3384, 1992). We have now used oriLyt as a reporter of HCMV DNA replication in a transient complementation assay in which cotransfected cosmid clones, instead of HCMV infection, provided essential trans-acting factors. Complemented replication was oriLyt dependent and phosphonoformic acid sensitive and produced tandem arrays typical of HCMV lytic-phase DNA synthesis. Thus, this assay provides a valid genetic test to find previously unidentified genes that are essential for DNA synthesis and to corroborate functional predictions made by nucleotide sequence comparisons and biochemical analyses. Five cosmids were necessary and sufficient to produce origin-dependent DNA synthesis; all but one of these required cosmids contain at least one candidate homolog of herpes simplex virus type 1 replication genes. We further used the assay to define essential regions in two of the required cosmids, pCM1017 and pCM1052. Results presented show that UL44, proposed on the basis of biochemical evidence to be the HCMV DNA polymerase accessory protein, was required for complementation. In addition, three genomic regions encoding regulatory proteins also were needed to produce origin-dependent DNA synthesis in this assay: (i)

IRS1/TRS1, which cooperates with the major immediate-early proteins to activate UL44 expression; (ii) UL36-38; and (iii) the major immediate-early ***region*** comprising ***IE1*** and IE2. Combined, these results unequivocally establish the utility of this approach for mapping HCMV replication genes. Thus, it will now be possible to define the set of HCMV genes necessary and sufficient for initiating and performing lytic-phase DNA synthesis as well as to identify those virus genes needed for their expression in human fibroblasts.

L6 ANSWER 7 OF 15 MEDLINE

AU Crump J W; Geist L J; Auron P E; Webb A C; Stinski M F; Hunninghake G W

TI The immediate early genes of ***human*** ***cytomegalovirus*** require only proximal promoter elements to upregulate expression of interleukin-1 beta.

SO Am J Respir Cell Mol Biol, (1992 Jun) 6 (6) 674-7.

Journal code: AOB. ISSN: 1044-1549.

AB ***Human*** ***cytomegalovirus*** (HCMV) can infect monocytes and macrophages. The immediate early one (IE1) gene product of HCMV positively regulates its own expression, as well as the expression of the interleukin-1 beta (IL-1) gene. This study describes the IL-1 promoter proximal region required for upregulation of IL-1 gene expression by the HCMV IE1 or IE1 plus IE2 gene products. An IL-1 chloramphenicol acetyltransferase (CAT) construct containing the IL-1 genomic upstream sequence from position -1097 to +14 and four additional IL-1CAT plasmids containing progressive deletions of the -1097 to -131 sequence were used to evaluate the effect of the HCMV IE gene products on IL-1 gene expression. IL-1CAT plasmids were transfected into a monocytic cell line, THP-1, with plasmids containing either the IE promoter-regulatory ***region*** upstream of the bona fide ***IE1*** (pIE1), IE2 (pIE2), or IE1+2 genes (pIE1+2) or a control plasmid containing the IE promoter-regulatory region alone (pLink760). In the presence of pIE1+2, there was an approximate 15-fold increase in CAT activity compared with the control, pLink760, in cells with CAT plasmids containing the -1097 to +14 IL-1 sequence. Plasmids with progressive deletions of this sequence, including the plasmid containing the shortest upstream segment (-131 to +14) also had an approximate 15-fold increase in CAT activity. The upregulation of IL-1 expression was mediated, primarily, by IE1 and not by IE2. This effect was promoter specific because an IL-1CAT plasmid with a complete deletion of the proximal promoter elements (-234 to +146) did not respond to the HCMV IE gene

products.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 8 OF 15 MEDLINE

AU Messerle M; Buhler B; Keil G M; Koszinowski U H

TI Structural organization, expression, and functional characterization of the murine cytomegalovirus immediate-early gene 3. SO J Virol, (1992 Jan) 66 (1) 27-36.

Journal code: KCV. ISSN: 0022-538X.

AB We have previously defined ie3 as a coding ***region*** located downstream of the ***ie1*** gene which gives rise to a 2.75-kb immediate-early (IE) transcript. Here we describe the structural organization of the ie3 gene, the amino acid sequence of the gene product, and some of the functional properties of the protein. The 2.75-kb ie3 mRNA is generated by splicing and is composed of four exons. The first three exons, of 300, 111, and 191 nucleotides (nt), are shared with the ie1 mRNA and are spliced to exon 5, which is located downstream of the fourth exon used by the ie1 mRNA. Exon 5 starts 28 nt downstream of the 3' end of the ie1 mRNA and has a length of 1,701 nt. The IE3 protein contains 611 amino acids, the first 99 of which are shared with the ie1 product pp89. The IE3 protein expressed at IE times has a relative mobility of 88 kDa in gels, and a mobility shift to 90 kDa during the early phase is indicative of posttranslational modification. Sequence comparison reveals significant homology of the exon 5-encoded amino acid sequence with the respective sequence of UL 122, a component of the IE1-IE2 complex of ***human*** ***cytomegalovirus*** (HCMV). This homology is also apparent at the functional level. The IE3 protein is a strong transcriptional activator of the murine cytomegalovirus (MCMV) e1 promoter and shows an autoregulatory function by repression of the MCMV ie1/ie3 promoter. The high degree of

conservation between the MCMV ie3 and HCMV IE2 genes and their products with regard to gene structure, amino acid sequence, and protein functions suggests that these genes play a comparable role in the transcriptional control of the two cytomegaloviruses.

L6 ANSWER 9 OF 15 MEDLINE

AU Tanaka J; Sadanari H; Sato H; Fukuda S

TI Sodium butyrate-inducible replication of ***human*** ***cytomegalovirus*** in a human epithelial cell line. SO Virology, (1991 Nov) 185 (1) 271-80.

Journal code: XEA. ISSN: 0042-6822.

AB Replication of ***human*** ***cytomegalovirus*** (HCMV) in a human epithelial thyroid papillary carcinoma cell line (TPC-1) was restricted. However, pretreatment of these cells with 5 mM sodium butyrate (NaB) for 24 hr before infection enhanced both HCMV yield and infectious center titer to a similar level of that seen in human embryonic lung fibroblast cells. Immunofluorescence staining, gel electrophoresis, and Northern blot analysis revealed that TPC-1 cells are nonpermissive for expression of HCMV major immediate early (IE1) functions, but many of the cells become permissive after being treated with NaB. The presence of cycloheximide during NaB pretreatment of the cells efficiently diminished the stimulatory effect of NaB on expression of the IE1 gene. Therefore, it appeared that NaB induces the synthesis of a cellular protein(s) which apparently plays an important role in the conversion of nonpermissive cells to a permissive state for expression of this critical viral gene. Transient chloramphenicol acetyltransferase (CAT) assay experiments indicated that in TPC-1 cells the HCMV-CAT construct which contains the complete ***IE1*** promoter regulatory ***region*** was expressed poorly, whereas a high level of CAT activity was detectable in the NaB-treated cells. Therefore, these results suggest that the enhancing effect of NaB on HCMV replication is expressed through some host cellular factor(s), and the HCMV ***IE1*** promoter regulatory ***region*** is most likely to be the primary target of NaB action.

L6 ANSWER 10 OF 15 MEDLINE

AU Alp N J; Allport T D; Van Zanten J; Rodgers B; Sissons J G; Borysiewicz L K

TI Fine specificity of cellular immune responses in humans to ***human*** ***cytomegalovirus*** immediate-early 1 protein. SO J Virol, (1991 Sep) 65 (9) 4812-20.

Journal code: KCV. ISSN: 0022-538X.

AB Cell-mediated immunity is important in maintaining the virus-host equilibrium in persistent ***human*** ***cytomegalovirus*** (HCMV) infection. The HCMV 72-kDa major immediate early 1 protein (IE1) is a target for CD8+ cytotoxic T cells in humans, as is the equivalent 89-kDa protein in mouse. Less is known about responses against this protein by CD4+ T cells, which may be important as direct effector cells or helper cells for antibody and CD8+ responses. Proliferative-T-cell responses to HCMV IE1 were studied in normal seropositive subjects. Peripheral blood mononuclear cells from 85% of seropositive subjects proliferated in response to HCMV from infected fibroblasts, and of these, 73% responded to recombinant baculovirus IE1. Responding cells were predominantly CD3+ CD4+. IE1 antigen preparations, including baculovirus recombinant protein, transfected rat cell nuclei, and synthetic peptides, induced IE1-specific T-cell lines which cross-reacted between the preparations. The fine specificity of these IE1-specific T-cell lines was studied by using overlapping synthetic peptides encompassing the entire sequence of the IE1 protein. The regions of the IE1 molecule recognized were identified and these varied between individuals, possibly reflecting differences in major histocompatibility complex (MHC) class II haplotype. In one subject, the peptide specificities of proliferative and MHC class I-restricted cytotoxic determinants on IE1 were spatially distinct. Thus, no single immunodominant T-cell determinant within HCMV IE1 was identified, suggesting that multiple peptides or a ***region*** of the 72-kDa ***IE1*** protein would be required to induce specific T-cell responses in humans.

L6 ANSWER 11 OF 15 MEDLINE

AU Malone C L; Vesole D H; Stinski M F

TI Transactivation of a ***human*** ***cytomegalovirus*** early promoter by gene products from the immediate-early gene IE2 and augmentation by IE1: mutational analysis of the viral proteins. SO J Virol, (1990 Apr) 64 (4) 1498-506.
Journal code: KCV. ISSN: 0022-538X.
AB Expression from a ***human*** ***cytomegalovirus*** early promoter (E1.7) has been shown to be activated in trans by the IE2 gene products (C.-P. Chang, C. L. Malone, and M. F. Stinski, J. Virol. 63:281-290, 1989). Using wild-type and mutant viral proteins, we have defined the protein regions required for transactivation of the E1.7 promoter in IE2 and for augmentation of transactivation in the IE1 protein. Two regions of the IE2 proteins were found to be essential for transactivation. One near the amino terminus is within 52 amino acids encoded by exon 3. The second comprises the carboxyl-terminal 85 amino acids encoded by exon 5. The IE2 protein encoded by an mRNA which lacks the intron within exon 5 and the IE2 protein encoded by exon 5 had no activity for transactivation of the E1.7 promoter. Although the IE1 gene product alone had no effect on this early viral promoter, maximal early promoter activity was detected when both IE1 and IE2 gene products were present. The IE1 protein positively regulated its enhancer-containing
promoter-regulatory ***region*** . The ***IE1*** protein alone increased the steady-state level of IE2 mRNA; therefore, IE1 and IE2 are synergistic for expression from the E1.7 promoter. Like the IE2 proteins, the IE1 protein requires for activity 52 amino acids encoded by exon 3. IE1 also requires amino acids encoded by exon 4. Since the IE1 and IE2 proteins have 85 amino acids in common at the amino-terminal end encoded by exons 2 and 3, the difference between these specific transactivators resides in their carboxyl-terminal amino acids encoded by exons 4 and 5, respectively.

L6 ANSWER 12 OF 15 MEDLINE
AU Lafemina R L; Pizzorno M C; Mosca J D; Hayward G S
TI Expression of the acidic nuclear immediate-early protein (IE1) of ***human*** ***cytomegalovirus*** in stable cell lines and its preferential association with metaphase chromosomes. SO Virology, (1989 Oct) 172 (2) 584-600.
Journal code: XEA. ISSN: 0042-6822.
AB Stable DNA-transfected Vero cell lines that express the major immediate-early nuclear antigen (IE68) of HCMV-(Towne) have been established. Immunofluorescence staining with monoclonal antibodies revealed that the protein was distributed either in a uniform diffuse nuclear pattern or as punctate nuclear granules in up to 80% of the cells in these cultures. In addition, 1 to 2% of the positive nuclei gave a distinctive staining pattern suggesting an association with the chromosomes of mitotic cells. Colcemid-blocking studies confirmed that most of the IE antigen was localized in the vicinity of condensed chromosomes in all metaphase cells after methanol fixation. In contrast, the SV40 large T-antigen protein was found to be preferentially excluded from metaphase chromosomes in a similar colcemid-treated human cell line. In transient expression assays, 1 to 2% of IE antigen-positive Vero, 293, or Balb/c3T3 cells also displayed a metaphase chromosome association pattern. Mapping studies using deletion and truncation mutants revealed that the monoclonal antibodies recognized epitopes encoded within the small NH2-terminal exons that are common to both the IE1 and IE2 gene products. However, an intact exon-4 ( ***IE1*** ) ***region*** , but not the exon-5 (IE2) region of the HCMV IE gene complex, was required for conferring both the normal diffuse nuclear localization pattern and the chromosome-association properties. Furthermore, removal of the glutamic acid-rich COOH-terminal coding portions of exon-4 resulted in aberrant staining patterns with production of large, phase-dense nuclear globules in all positive cells. An association between the IE68 IE1 protein and metaphase chromosomes was also detected after HCMV-(Towne) infection in a small proportion of both nonpermissive Balb/c3T3 cells and permissive HF cells. We conclude that the IE1 acidic nuclear phosphoprotein displays some properties similar to those of the EBNA-1 protein of Epstein-Barr virus and suggest that it may potentially play a role in maintenance of the latent state of HCMV DNA.

L6 ANSWER 13 OF 15 MEDLINE
AU Pizzorno M C; O'Hare P; Sha L; LaFemina R L; Hayward G S TI trans-activation and autoregulation of gene expression by the immediate-early region 2 gene products of ***human*** ***cytomegalovirus*** .
SO J Virol, (1988 Apr) 62 (4) 1167-79.
Journal code: KCV. ISSN: 0022-538X.
AB The major immediate-early (IE) gene region mapping at coordinates 0.71 to 0.74 in the genome of ***human***
***cytomegalovirus*** (HCMV) gives rise to a series of overlapping spliced IE mRNAs that are all under the transcriptional control of the complex IE68 promoter-enhancer region. We show here that one of the phosphorylated nuclear proteins encoded by this region behaves as a powerful but nonspecific trans-activator of gene expression. In transient chloramphenicol acetyltransferase (CAT) assay experiments with Vero cells all relatively weak heterologous target promoters tested, including those of herpes simplex virus IE175 and delayed-early genes, adenovirus E3, the enhancerless simian virus 40 early gene, and the human beta interferon gene, were stimulated between 30- and 800-fold by cotransfection with the HindIII C fragment of HCMV (Towne) DNA. In contrast, expression of the homologous HCMV IE68-CAT gene but not SV2-CAT was specifically repressed. Inactivation mapping studies of the effector DNA, together with dose-response comparisons with subclones from the region, revealed that an intact 7.1-kilobase sequence encompassing both the IE1 and IE2 coding regions (exons 1 to 5) in the major IE transcription complex was required for both the nonspecific trans-activation and autoregulatory responses. The ***IE1*** coding ***region*** alone (exons 1 to 4) was inactive, but both functions were restored by insertion of the IE2 coding region (exon 5) in the correct orientation downstream from the ***IE1*** coding ***region*** . Internal deletions or inserted terminator codons in IE1 (exon 4) still gave efficient trans-activation and autoregulation, whereas the insertion of terminator codons in IE2 (exon 5) abolished both activities. Finally, IE2 (exon 5) sequences only (under the direct transcriptional control of the strong simian CMV IE94 promoter) were still able to specifically down regulate IE68-CAT expression but failed to exhibit trans-activation properties. Therefore, the IE2 gene product(s) of HCMV appear likely to be key control proteins involved in gene regulation during HCMV infection.

L6 ANSWER 14 OF 15 MEDLINE
AU Tevethia M J; Spector D J; Leisure K M; Stinski M F
TI Participation of two ***human*** ***cytomegalovirus*** immediate early gene regions in transcriptional activation of adenovirus promoters.
SO Virology, (1987 Dec) 161 (2) 276-85.
Journal code: XEA. ISSN: 0042-6822.
AB The participation of ***human*** ***cytomegalovirus*** (HCMV) immediate early genes in the activation of the expression of adenovirus genes in trans (trans-activation) was examined. The initial strategy used was to determine the ability of HCMV genes to complement mutants of adenovirus E1a, an immediate early gene which encodes a trans-activator. The HCMV immediate early gene regions IE1 and IE2 complemented E1a-deficient mutants in three separate assays. IE1 and IE2 substituted for E1a in the synthesis of infectious adenovirus, late adenovirus RNA, and adenovirus DNA. Complementation by the IE2 gene ***region*** alone, but not by ***IE1*** alone, was observed using the most discriminating assay, that for late adenovirus RNA synthesis. A role for both HCMV gene regions in positive transcriptional control was indicated by their ability to increase expression of chloramphenicol acetyltransferase (CAT) mediated by the adenovirus E2a promoter. The IE2 ***region*** alone activated CAT synthesis but ***IE1*** alone had no detectable activity. Moreover, the activity of both gene regions was about 10-fold higher than that of IE2 alone. These data indicate that efficient complementation of E1a-deficient mutants and trans-activation of adenovirus early promoters involved the participation of both HCMV immediate early gene regions.
L6 ANSWER 15 OF 15 MEDLINE

AU Hennighausen L; Fleckenstein B
TI Nuclear factor 1 interacts with five DNA elements in the promoter region of the ***human*** ***cytomegalovirus*** major immediate early gene.
SO EMBO J, (1986 Jun) 5 (6) 1367-71.
Journal code: EMB. ISSN: 0261-4189.
AB The ***human*** ***cytomegalovirus*** (HCMV), a ubiquitous pathogen of the herpesvirus group, has a linear double-stranded DNA genome of 235 kb. The expression of its major immediate early gene (IE1) is entirely dependent on host factors, presumably proteins binding to DNA elements in the regulatory regions of the gene. We have identified four high-affinity binding sites for nuclear factor 1 (NF1) in the promoter upstream ***region*** of ***IE1*** gene between nucleotides -780 and -610, and an additional, even stronger, binding site in the first intron near nucleotide +350. NF1 activity is found in a wide range of species and binds to the sequence 5' TGGC/ANNNNNGCCAA3' on double-stranded DNA, protecting approximately 25 bp from DNase I digestion; its functional importance has been found first in the necessity for adenovirus DNA replication, where it may be important in mediating the binding of other proteins. The regulatory significance of NF1 recognition elements within other genes is unknown. The NF1 binding sites in the HCMV IE1 gene coincide with regions that had been shown to be sensitive to DNase I in the active gene but not sensitive in the silent gene; there was, however, no NF1 binding in the strong and constitutively DNase I-hypersensitive transcription enhancer of the IE1 gene. This suggests that the specific protein--DNA interaction described is important in the regulated control of the IE1 gene.
=> d his

(FILE 'HOME' ENTERED AT 15:30:47 ON 02 JUN 95)
SET PAGELENGTH SCROLL

FILE 'MEDLINE' ENTERED AT 15:31:28 ON 02 JUN 95
L1 74 S HUMAN CYTOMEGALOVIRUS IMMEDIATE EARLY
L2 74 SORT L1 PY
L3 1859 S HUMAN CYTOMEGALOVIRUS
L4 0 S 1E1 REGION
L5 22 S (IE1 REGION) OR REGION(5A)IE1
L6 15 S L5 AND L3

=> s ie region 1
5832 IE
176781 REGION
1456771 1
L7 4 IE REGION 1
(IE(W)REGION(W)1)

=> s l7 and l3
L8 4 L7 AND L3

=> d au,ti,so,ab 1-4

L8 ANSWER 1 OF 4 MEDLINE
AU Plachter B; Britt W; Vornhagen R; Stamminger T; Jahn G TI Analysis of proteins encoded by IE regions 1 and 2 of ***human*** ***cytomegalovirus*** using monoclonal antibodies generated against recombinant antigens.
SO Virology, (1993 Apr) 193 (2) 642-52.
Journal code: XEA. ISSN: 0042-6822.

AB The genomic region of ***human*** ***cytomegalovirus*** (HCMV) encoding the major immediate-early (IE) proteins was cloned as overlapping fragments into a prokaryotic expression vector. Three recombinant polypeptides were used as antigens to generate monoclonal antibodies specifically reactive with the proteins encoded by ***IE*** ***region*** ***1*** and IE region 2. At least 10 different antigenic regions were identified on the IE proteins of HCMV. One monoclonal generated against an IE-2 polypeptide of 156 amino acids (termed SMX) was found to react with a viral pentapeptide, which was also a constituent of the beta-chain of human HLA-DR. This peptide was contained in the 40-kDa (p40) protein encoded by IE region 2. This protein appeared to be an abundant product of the major IE region in infected cells at late times after infection. The putative translation initiation site for p40 was mapped to position 3348 of the IE2 sequence using monoclonal antibody SMX. It is therefore proposed that p40 consists of amino acids 242-580 encoded by the IE2 gene of HCMV (strain AD169). Neither this late protein nor any other of the IE1/IE2-encoded proteins was detectable in extracellular virions.

L8 ANSWER 2 OF 4 MEDLINE
AU Stenberg R M; Depto A S; Fortney J; Nelson J A
TI Regulated expression of early and late RNAs and proteins from the ***human*** ***cytomegalovirus*** immediate-early gene region. SO J Virol, (1989 Jun) 63 (6) 2699-708.
Journal code: KCV. ISSN: 0022-538X.
AB Expression of RNA and protein from the ***human*** ***cytomegalovirus*** immediate-early (IE) gene region (map units 0.732 to 0.751) was analyzed at early and late times after infection. The level of RNA present at late times (48 to 72 h after infection) was significantly higher than that present at IE times (5 h after infection). The profile of IE RNA in the cytoplasm of infected cells was different from that previously reported on polysomes (R. M. Stenberg, P. R. Witte, and M. F. Stinski, J. Virol. 56:665-675, 1985). The data indicate that the 1.95-kilobase (kb) major ***IE*** ***region*** ***1*** mRNA, which codes for the 72-kilodalton (kDa) protein, and the 1.7-kb IE region 2 (IE2) spliced mRNA, which codes for the IE2 55-kDa protein, may be preferentially associated with polysomes. However, the IE2 2.2-kb unspliced mRNA, which codes for an 86-kDa protein, may be preferentially excluded. This RNA was abundant in the cytoplasm under IE conditions but was not present on polysomes in significant quantities. This indicates that IE gene products may be involved in translational control of cytomegalovirus RNA. At late times, new transcription takes place within region 2. A 1.5-kb RNA is transcribed from a late promoter in region 2 that apparently does not function in cells infected with DNA-negative mutant ts66. These results demonstrate that the IE gene region is transcribed throughout infection and that multiple levels of regulation exist.
L8 ANSWER 3 OF 4 MEDLINE
AU Stenberg R M; Witte P R; Stinski M F
TI Multiple spliced and unspliced transcripts from ***human*** ***cytomegalovirus*** immediate-early region 2 and evidence for a common initiation site within immediate-early region 1. SO J Virol, (1985 Dec) 56 (3) 665-75.
Journal code: KCV. ISSN: 0022-538X.
AB ***Human*** ***cytomegalovirus*** immediate-early (IE) region 2 (0.732 to 0.740 map unit) begins 35 nucleotides downstream of ***IE*** ***region*** ***1*** (Stenberg et al., J. Virol. 49:190-199, 1984). A series of mRNAs that have different splicing patterns are transcribed from region 2. There is an unspliced 1,589-nucleotide exon present in minor amounts and two spliced exons (836 and 289 nucleotides) present in larger amounts. The IE region 2 exons were found to be spliced onto the first three exons of region 1. Therefore, under IE conditions the region 1 promoter-regulatory region can promote transcription of region 2. Promoter sequences (i.e., CAAT and TATA boxes) are found upstream of the 5' end of IE region 2 but presumably function poorly at IE times after infection. The transcriptional regulation of these IE genes and the possible functional roles of the proteins are discussed. We postulate that a series of unique but related proteins are made from the region 2 transcripts. Some of these proteins should contain the same 169 amino-terminal residues as the major IE 72-kilodalton protein encoded by ***IE***

***region*** ***1*** (Stenberg et al., J. Virol. 49:190-199, 1984). Variations in the amino acid sequences of the region 2 proteins could occur at either the amino terminus, the carboxy terminus, or both termini.

L8 ANSWER 4 OF 4 MEDLINE

AU Thomsen D R; Stenberg R M; Goins W F; Stinski M F

TI Promoter-regulatory region of the major immediate early gene of ***human*** ***cytomegalovirus*** .

SO Proc Natl Acad Sci U S A, (1984 Feb) 81 (3) 659-63. Journal code: PV3. ISSN: 0027-8424.

AB The DNA templates containing immediate early (IE) genes of ***human*** ***cytomegalovirus*** (CMV) were transcribed in vitro by using a HeLa cell extract. When ***IE*** ***region*** ***1*** , 2, and 3 were used, transcription was detected qualitatively only from ***IE*** ***region*** ***1*** . Transcription was detected with DNA representing IE region 2 when the ***IE*** ***region*** ***1*** promoter was not present. DNA sequence analysis of the upstream regulatory region of ***IE*** ***region*** ***1*** detected two distinct repeats of 19 and 18 nucleotides, both being repeated four times. A putative cruciform structure could form through the surrounding sequences with each 18-nucleotide repeat being located in the unpaired region. The potential secondary structure and the repeat sequences in the regulatory region of ***IE*** ***region*** ***1*** are presumably related to the high level of transcription of this IE gene.

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967 POLYADENYLATION
104 SV40 POLYADENYLATION
(SV40(W)POLYADENYLATION)
L2 16 SV40 ORIGIN(P)SV40 POLYADENYLATION

=> d 1-16

1. 5,414,071, May 9, 1995, Human cytokine IL-9; Yu-Chung Yang, et al., 530/351; 424/85.2; 930/141 [IMAGE AVAILABLE]

2. 5,371,193, Dec. 6, 1994, Mammalian cytokine, IL-11; Frances K. Bennett, et al., 530/351; 424/85.1; 435/69.52; 930/141 [IMAGE AVAILABLE]
3. 5,366,729, Nov. 22, 1994, Non-glycosylated variants of extracellular superoxide dismutase (EC-SOD); Stefan Marklund, et al., 424/94.4; 435/189, 240.2, 320.1; 536/23.2 [IMAGE AVAILABLE]

4. 5,326,558, Jul. 5, 1994, Megakaryocytopoietic factor; Katherine Turner, et al., 424/85.1; 530/350, 351, 820, 827; 930/140, 145 [IMAGE AVAILABLE]

5. 5,312,732, May 17, 1994, Hormone receptor compositions and methods; Ronald M. Evans, et al., 435/69.1, 240.2, 252.3, 320.1; 536/23.5 [IMAGE AVAILABLE]

6. 5,298,429, Mar. 29, 1994, Bioassay for identifying ligands for steroid hormone receptors; Ronald M. Evans, et al., 436/501; 435/69.1, 172.3, 252.3, 320.1 [IMAGE AVAILABLE]

7. 5,298,400, Mar. 29, 1994, Polynucleotide constructs for secreted glycosylated plasminogen activator inhibitor-2 (PAI-2); Peter L. Whitfeld, et al., 435/69.8, 69.2, 172.3, 240.1, 240.2, 320.1 [IMAGE AVAILABLE]

8. 5,260,417, Nov. 9, 1993, Megakaryocyte growth promoting activity protein; Barbara W. Grant, et al., 530/351; 424/85.1; 530/399 [IMAGE AVAILABLE]

9. 5,248,603, Sep. 28, 1993, Superoxide dismutase; Stefan Marklund, et al., 435/189, 240.2, 320.1; 536/23.2 [IMAGE AVAILABLE]

10. 5,215,895, Jun. 1, 1993, DNA encoding a mammalian cytokine, interleukin-11; Frances K. Bennett, et al., 435/69.52, 69.5, 172.3, 240.1, 243, 252.3, 320.1; 536/23.5; 935/22, 52, 60, 66 [IMAGE AVAILABLE]
11. 5,171,568, Dec. 15, 1992, Recombinant herpes simplex gb-gd vaccine; Rae L. Burke, et al., 424/186.1, 231.1, 279.1, 283.1, 450, 812; 435/69.3, 172.3, 235.1, 320.1; 514/8; 536/23.72 [IMAGE AVAILABLE]

12. 5,156,949, Oct. 20, 1992, Immunoassays for antibody to human immunodeficiency virus using recombinant antigens; Paul A. Luciw, et al., 435/5, 7.2, 69.1, 172.3, 252.33, 810, 820, 974; 935/60, 66, 69, 71 [IMAGE AVAILABLE]

13. 5,130,245, Jul. 14, 1992, Superoxide dismutase; Stefan Marklund, et al., 435/189, 240.2, 320.1; 536/23.2; 935/14, 22, 70 [IMAGE AVAILABLE]
14. 5,071,773, Dec. 10, 1991, Hormone receptor-related bioassays; Ronald M. Evans, et al., 436/501; 435/69.7, 172.3 [IMAGE AVAILABLE]
15. 5,045,455, Sep. 3, 1991, Factor VIII:C cDNA cloning and expression; George Kuo, et al., 435/69.6, 69.1, 172.3, 240.2, 252.3, 252.33, 320.1; 536/23.51; 935/11, 27, 29, 32, 56, 60, 70, 73 [IMAGE AVAILABLE]
16. 4,798,789, Jan. 17, 1989, cDNA clones coding for polypeptides exhibiting murine interleukin-2 activity; Frank D. Lee, et al., 435/69.52, 172.3, 252.33, 320.1; 530/351; 536/23.5, 23.51, 24.1; 930/141 [IMAGE AVAILABLE]

=> s cytomegalovirus immediate early
967 CYTOMEGALOVIRUS
71107 IMMEDIATE
72116 EARLY
L3 26 CYTOMEGALOVIRUS IMMEDIATE EARLY
(CYTOMEGALOVIRUS(W)IMMEDIATE(W)EARLY)

=> d 1-26

1. 5,416,192, May 16, 1995, Epithelins: novel cysteine-rich growth modulating proteins; Mohammed Shoyab, et al., 530/324; 435/69.1; 530/399 [IMAGE AVAILABLE]

2. 5,385,839, Jan. 31, 1995, Transfer vectors and microorganisms containing human **cytomegalovirus** **immediate**-**early** promoter regulatory DNA sequence; Mark F. Stinski, 435/240.2, 69.1, 252.3, 252.33, 320.1 [IMAGE AVAILABLE]

3. 5,366,874, Nov. 22, 1994, Molecular cloning and expression of biologically-active diphtheria toxin receptor; Leon Eidels, et al., 435/69.1, 7.1, 7.2, 252.3, 320.1; 536/23.5 [IMAGE AVAILABLE]
4. 5,352,587, Oct. 4, 1994, Compositions and methods for the synthesis of natriuretic protein receptor B and methods of use; Ming-Shi Chang, et al., 435/69.1, 172.1, 240.1, 320.1; 514/12; 530/350 [IMAGE AVAILABLE]
5. 5,324,664, Jun. 28, 1994, Herpes virus thymidien kinase-encoding DNA; Jack H. Nunberg, et al., 435/320.1, 69.1, 172.1, 172.3, 235.1; 530/350; 536/23.1, 23.72, 24.1 [IMAGE AVAILABLE]

6. 5,324,663, Jun. 28, 1994, Methods and products for the synthesis of oligosaccharide structures on glycoproteins, glycolipids, or as free molecules, and for the isolation of cloned genetic sequences that determine these structures; John B. Lowe, 435/320.1, 69.1, 70.3, 172.3, 193, 240.2; 536/23.2; 935/14, 32, 70 [IMAGE AVAILABLE]

7. 5,302,706, Apr. 12, 1994, Senescent cell derived inhibitors of DNA synthesis; James R. Smith, 536/23.1; 435/4, 6, 69.1, 172.1, 240.2; 530/350; 536/23.4, 23.5 [IMAGE AVAILABLE]

8. 5,302,517, Apr. 12, 1994, Method of controlling the expression of a gene in a cell culture, cell culture vector used in the method and method of making the vector; Solon L. Rhode, III, 435/69.1, 172.3, 240.2; 935/11, 33, 34 [IMAGE AVAILABLE]

9. 5,273,876, Dec. 28, 1993, Recombinant human cytomegalovirus containing foreign gene; Lisa J. Hock, et al., 435/235.1, 69.1, 172.3, 320.1 [IMAGE AVAILABLE]

10. 5,262,319, Nov. 16, 1993, Method for obtaining bone marrow free of tumor cells using transforming growth factor .beta.3; Kenneth K. Iwata, et al., 435/240.2, 240.25; 530/399 [IMAGE AVAILABLE]

11. 5,256,642, Oct. 26, 1993, Compositions of soluble complement receptor 1 (CR1) and a thrombolytic agent, and the methods of use thereof; Douglas T. Fearon, et al., 514/8; 424/94.63, 94.64; 435/215, 216; 514/2; 530/350 [IMAGE AVAILABLE]

12. 5,242,819, Sep. 7, 1993, DNA molecules encoding hybrid proteins of tissue plasminogen activator and urokinase; Bhanu Rajput, et al., 435/240.2, 215, 226, 254.2, 320.1; 536/23.2, 23.4 [IMAGE AVAILABLE]

13. 5,219,990, Jun. 15, 1993, Papillomavirus E2 trans-activation repressors; Elliot J. Androphy, et al., 530/350, 300, 324, 826; 930/220 [IMAGE AVAILABLE]

14. 5,212,071, May 18, 1993, Nucleic acids encoding a human C3b/C4b receptor (CR1); Douglas T. Fearon, et al., 435/69.1, 252.3, 320.1; 530/350 [IMAGE AVAILABLE]

15. 5,190,756, Mar. 2, 1993, Methods and materials for expression of human plasminogen variant; Francis J. Castellino, et al., 424/94.64; 435/216, 217, 226; 514/822 [IMAGE AVAILABLE]

16. 5,168,062, Dec. 1, 1992, Transfer vectors and microorganisms containing human **cytomegalovirus** **immediate**-**early** promoter-regulatory DNA sequence; Mark F. Stinski, 435/240.2, 252.3, 252.33, 320.1 [IMAGE AVAILABLE]

17. 5,156,949, Oct. 20, 1992, Immunoassays for antibody to human immunodeficiency virus using recombinant antigens; Paul A. Luciw, et al., 435/5, 7.2, 69.1, 172.3, 252.33, 810, 820, 974; 935/60, 66, 69, 71 [IMAGE AVAILABLE]

18. 5,147,788, Sep. 15, 1992, Baculovirus vectors and methods of use; Martin J. Page, et al., 435/69.1, 69.3, 69.51, 69.7, 172.3, 320.1; 935/34, 60 [IMAGE AVAILABLE]

19. 5,124,263, Jun. 23, 1992, Recombination resistant retroviral helper cell and products produced thereby; Howard M. Temin, et al., 435/240.2, 172.3, 236, 320.1, 948; 935/32, 34, 57, 70, 71 [IMAGE AVAILABLE]

20. 5,122,458, Jun. 16, 1992, Use of a bGH gDNA polyadenylation signal in expression of non-bGH polypeptides in higher eukaryotic cells; Leonard E. Post, et al., 435/69.1, 69.2, 240.1, 240.2, 320.1; 536/23.51, 24.1; 935/6, 34, 70 [IMAGE AVAILABLE]

21. 5,087,572, Feb. 11, 1992, DNA encoding human plasminogen modified at the cleavage site; Francis J. Castellino, et al., 435/240.2, 217, 252.3, 320.1; 536/23.51 [IMAGE AVAILABLE]

22. 5,082,670, Jan. 21, 1992, Method of grafting genetically modified cells to treat defects, disease or damage or the central nervous system; Fred H. Gage, et al., 424/520, 570; 435/172.3, 240.2, 948; 514/44; 935/62, 70 [IMAGE AVAILABLE]

23. 5,081,028, Jan. 14, 1992, Preparation of transformed hosts which express binding factor related polypeptides; Hans Hofstetter, et al., 435/172.3, 69.5, 240.2, 252.3, 252.33; 930/140; 935/11, 28, 29, 32, 69, 70, 73 [IMAGE AVAILABLE]

24. 4,963,481, Oct. 16, 1990, Promoter system; Jean P. deVilliers, 435/69.1, 70.1, 172.3, 320.1; 536/23.5, 24.1; 935/32, 36, 60, 70 [IMAGE AVAILABLE]

25. 4,818,678, Apr. 4, 1989, Diagnostic system for the detection of cytomegalovirus; Michael B. A. Oldstone, et al., 435/5, 7.24, 29, 172.2, 240.27, 810; 436/512, 548; 530/388.3, 391.3, 808; 935/103, 110 [IMAGE AVAILABLE]

26. 4,783,399, Nov. 8, 1988, Diagnostic system for the detection of cytomegalovirus; Michael B. A. Oldstone, et al., 435/5, 7.24, 29, 172.2, 188, 240.27, 810; 436/512, 548; 530/388.3, 391.3, 808, 866; 935/103, 110 [IMAGE AVAILABLE]

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1. 5,156,949, Oct. 20, 1992, Immunoassays for antibody to human immunodeficiency virus using recombinant antigens; Paul A. Luciw, et al., 435/5, 7.2, 69.1, 172.3, 252.33, 810, 820, 974; 935/60, 66, 69, 71 [IMAGE AVAILABLE]

=> d kwic l3 24

US PAT NO: 4,963,481 [IMAGE AVAILABLE] L3: 24 of 26
SUMMARY:

BSUM(7)

More . . . protein operatively linked to the approximately 2.27 kilobase pair Pst I restriction fragment of the mCMV genome containing the mouse **cytomegalovirus** **immediate** **early** promoter or to an effective expression promoting fragment thereof. The fragment may comprise the 1387 base pair (bp) Hpa I/Pst. . .

=> d kwic l3 16,21

US PAT NO: 5,168,062 [IMAGE AVAILABLE] L3: 16 of 26 TITLE: Transfer vectors and microorganisms containing human **cytomegalovirus** **immediate**-**early** promoter-regulatory DNA sequence

US PAT NO: 5,087,572 [IMAGE AVAILABLE] L3: 21 of 26
DETDESC:

DETD(78)

pRK-tPA drives the efficient synthesis of t-PA upon transient transfection into human 293 fibroblasts. The vector contains the **cytomegalovirus** **immediate** **early** gene enhancer and promoter, the CMV-IE splice donor site and a portion of the associated intron, the bacteriophage SP6 promoter,. . .

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US PAT NO: 5,168,062 [IMAGE AVAILABLE] L3: 16 of 26 DATE ISSUED: Dec. 1, 1992
TITLE: Transfer vectors and microorganisms containing human **cytomegalovirus** **immediate**-**early** promoter-regulatory DNA sequence
INVENTOR: Mark F. Stinski, Iowa City, IA
ASSIGNEE: University of Iowa Research Foundation, Oakdale, IA (U.S. corp.)
APPL-NO: 07/582,130
DATE FILED: Sep. 10, 1990
REL-US-DATA: Continuation of Ser. No. 256,134, Oct. 5, 1988, abandoned, which is a continuation of Ser. No. 58,662, May 22, 1987, abandoned, which is a continuation of Ser. No. 696,617, Jan. 30, 1985, abandoned.
INT-CL: [5] C12N 5/10; C12N 15/00; C12N 15/86; C12N 1/21 US-CL-ISSUED: 435/240.2, 320.1, 252.3, 252.33; 536/27
US-CL-CURRENT: 435/240.2, 252.3, 252.33, 320.1
SEARCH-FLD: 435/320.1, 252.3, 252.33; 536/27
REF-CITED:

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of the Early Viral Genes", Molecular and Cellular Biology 3:1222-1234, 1983.
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This invention was made with Government support under Grant No. AI13526 awarded by the National Institute of Allergy and Infectious Diseases. The Government has certain rights in this invention.
ART-UNIT: 185
PRIM-EXMR: Richard A. Schwartz
ASST-EXMR: S. C. Nolan
LEGAL-REP: Seed and Berry

ABSTRACT:
The cloning of a eucaryotic promoter-regulatory region that functions preferentially in human cells is disclosed. The invention is exemplified by the cloning of a section of the human cytomegalovirus genome comprising a DNA sequence with regulatory and promoter signals and an initiation site for RNA synthesis. The fragment, termed the human cytomegalovirus (HCMV) promoter-regulatory sequence, was obtained from purified HCMV DNA.
8 Claims, 3 Drawing Figures

US PAT NO: 5,087,572 [IMAGE AVAILABLE] L3: 21 of 26 DATE ISSUED: Feb. 11, 1992
TITLE: DNA encoding human plasminogen modified at the cleavage site
INVENTOR: Francis J. Castellino, Granger, IN
Deborah L. Higgins, San Carlos, CA
ASSIGNEE: Genentech, Inc., South San Francisco, CA (U.S. corp.) APPL-NO: 07/444,584
DATE FILED: Dec. 1, 1989
INT-CL: [5] C12N 15/57; C12N 15/00; C12N 5/10; C12N 1/21; C12N 1/19
US-CL-ISSUED: 435/240.2, 217, 252.3, 255, 320.1; 536/27
US-CL-CURRENT: 435/240.2, 217, 252.3, 320.1; 536/23.51
SEARCH-FLD: 536/27; 435/217, 320, 240.2, 212, 215, 255, 252.3, 320.1; 424/94.64
REF-CITED:

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0028489 5/1981 European Patent Office
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0293934 12/1988 European Patent Office
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ART-UNIT: 185
PRIM-EXMR: Richard A. Schwartz
ASST-EXMR: Marianne Porta
LEGAL-REP: Ginger R. Dreger, Janet E. Hasak

ABSTRACT:
A cleavage-resistant plasminogen molecule is provided that is conveniently produced in recombinant cells by expression of a nucleic acid sequence encoding the plasminogen molecule. Preferably the plasminogen is a sequence variant with a modification in its two-chain cleavage site. The plasminogen molecule may be purified, acylated, complexed with acylated or non-acylated fibrinolytic enzymes, and formulated into pharmaceutical compositions for use in thrombolytic therapy.

12 Claims, 23 Drawing Figures

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45642 IMMEDIATE
13915 CYTOMEGALOVIRUS
11259 INTRON?
10458 SPLIC?
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L2 ANSWER 1 OF 47 MEDLINE
TI Post-transcriptional control of human cytomegalovirus gene expression.

L2 ANSWER 2 OF 47 MEDLINE
TI Abundant constitutive expression of the immediate-early 94K protein from cytomegalovirus (Colburn) in a DNA-transfected mouse cell line.
L2 ANSWER 3 OF 47 MEDLINE
TI Structural analysis of the major immediate early gene of human cytomegalovirus.

L2 ANSWER 4 OF 47 MEDLINE
TI Structure of the transforming region of human cytomegalovirus AD169.
L2 ANSWER 5 OF 47 MEDLINE
TI Multiple ***spliced*** and unspliced transcripts from human ***cytomegalovirus*** ***immediate*** -early region 2 and evidence for a common initiation site within ***immediate*** -early region 1.

L2 ANSWER 6 OF 47 MEDLINE
TI The structure of the major immediate early gene of human cytomegalovirus strain AD169.

L2 ANSWER 7 OF 47 MEDLINE
TI Analysis of the major transcripts encoded by the long repeat of human cytomegalovirus strain AD169.

L2 ANSWER 8 OF 47 MEDLINE
TI Nuclear factor 1 interacts with five DNA elements in the promoter region of the human cytomegalovirus major immediate early gene.
L2 ANSWER 9 OF 47 MEDLINE
TI Identification and characterization of the human cytomegalovirus immediate-early region 2 gene that stimulates gene expression from an inducible promoter.

L2 ANSWER 10 OF 47 MEDLINE
TI Sequence and structural organization of murine cytomegalovirus immediate-early gene 1.

=> d au,ti,so,ab 1,6

L2 ANSWER 1 OF 47 MEDLINE

AU DeMarchi J M
TI Post-transcriptional control of human cytomegalovirus gene expression.
SO Virology, (1983 Jan 30) 124 (2) 390-402.
Journal code: XEA. ISSN: 0042-6822.
AB During the ***immediate*** -early, early, and late phases of human ***cytomegalovirus*** infection in human fibroblasts, transcripts accumulated, respectively, from approximately 20, 75, and 90% of the sequences on the genome. Not all of the sequences which accumulated during the ***immediate*** -early and early phases were represented on polysomes, however. Four transcripts synthesized in cycloheximide-treated cells were studied in detail. A 2.2-kb transcript (0.713-0.733 map units) represented 95% of the polysome-associated RNA in cycloheximide-treated cells and was the first to be detected on polysomes at 2 hr postinfection in untreated cells. A second, less abundant, transcript of 5.2 kb (0.670-0.733 map units) was also found on polysomes in cycloheximide-treated cells, and preliminary evidence suggested that this transcript may be ***spliced*** during processing. A 3.25-kb transcript (0.190-0.217 map units) was identified also as a minor polysome-associated species of RNA. One transcript of 4.8 kb (0.630-0.670) remained associated with the nucleus and was not processed into mRNA in cycloheximide-treated cells. Differential stability between the various transcripts was observed, the 2.2-kb transcript being the most stable. The results showed that in human ***cytomegalovirus*** -infected cells controls exist at the level of transcript accumulation, transport into the cytoplasm, preferential association with polysomes, and relative stability of RNAs.

L2 ANSWER 6 OF 47 MEDLINE
AU Akrigg A; Wilkinson G W; Oram J D
TI The structure of the major immediate early gene of human cytomegalovirus strain AD169.
SO Virus Res, (1985 Mar) 2 (2) 107-21.
Journal code: X98. ISSN: 0168-1702.
AB The nucleotide sequence of the major ***immediate*** early (IE) gene of human ***cytomegalovirus*** strain AD169 was determined. The structure of the gene was examined by nuclease mapping and by sequence analysis of a cDNA clone made from IE mRNA. The gene encodes a ***spliced*** molecule of 1736 nucleotides, made up of four exon sequences of 121, 88, 185 and 1342 nucleotides. Three ***introns*** (827, 114 and 170n) were located near the 5' end of the gene. A single open reading frame starting in the second exon extends for 491 amino acids, corresponding to a protein of molecular weight 64000. The putative promoter region contains several short direct and inverted repeat sequences of 16, 18, 19 and 21 nucleotides, which extend 509n upstream from the transcription start site. The structure of the major IE gene and its protein product are discussed and compared with the corresponding IE gene from the Towne strain of HCMV.

=> d ti 11-20

L2 ANSWER 11 OF 47 MEDLINE
TI Novel induction by herpes simplex virus of hybrid interferon gene transcripts driven by the strong cytomegalovirus IE94 promoter.
L2 ANSWER 12 OF 47 MEDLINE
TI Abundant 5 kb RNA of human cytomegalovirus without a major translational reading frame.

L2 ANSWER 13 OF 47 MEDLINE
TI Identification of sequence requirements and trans-acting functions necessary for regulated expression of a human cytomegalovirus early gene.

L2 ANSWER 14 OF 47 MEDLINE
TI trans-activation and autoregulation of gene expression by the immediate-early region 2 gene products of

human cytomegalovirus.
L2 ANSWER 15 OF 47 MEDLINE
TI An enhancer element in the short unique region of human cytomegalovirus regulates the production of a group of abundant immediate early transcripts.

L2 ANSWER 16 OF 47 MEDLINE
TI Regulated expression of early and late RNAs and proteins from the human cytomegalovirus immediate-early gene region.

L2 ANSWER 17 OF 47 MEDLINE
TI Detection of mRNA from the immediate early gene of human cytomegalovirus in infected cells by in vitro amplification.
L2 ANSWER 18 OF 47 MEDLINE
TI New vectors for the efficient expression of mammalian genes in cultured cells.

L2 ANSWER 19 OF 47 MEDLINE
TI Characterization of the murine cytomegalovirus early transcription unit e1 that is induced by immediate-early proteins.
L2 ANSWER 20 OF 47 MEDLINE
TI Promoter-specific trans activation and repression by human cytomegalovirus immediate-early proteins involves common and unique protein domains.

=> d 11,15,18 au,ti,so,ab

L2 ANSWER 11 OF 47 MEDLINE
AU Mosca J D; Jeang K T; Pitha P M; Hayward G S
TI Novel induction by herpes simplex virus of hybrid interferon gene transcripts driven by the strong cytomegalovirus IE94 promoter. SO J Virol, (1987 Mar) 61 (3) 819-28.
Journal code: KCV. ISSN: 0022-538X.
AB We have constructed stable DNA-transfected LTK+ cell lines containing two different coselected hybrid interferon (IFN) genes driven by the usually strong and constitutive promoter from the ***immediate*** -early 94K protein (IE94) gene of simian ***cytomegalovirus*** . Surprisingly, and unlike hybrid IE94-chloramphenicol acetyltransferase gene constructs, both of the IE94-IFN genes (one with and one without the complex ***spliced*** ***intron*** region) produced relatively low basal titers of biologically active human IFN in the mouse cell lines. However, IFN expression could be stimulated up to 120-fold by superinfection with herpes simplex virus (HSV), although not with ***cytomegalovirus*** . To examine the mechanism of this unexpected HSV induction process, we measured the levels of both IE94-IFN mRNA and IFN protein produced under various infection protocols. Compared with similar previously characterized cell lines containing hybrid IFN genes under the control of HSV IE or delayed-early (DE) promoters, activation of IFN expression first occurred at an intermediate time. Both IE94-IFN cell lines also produced an unusual pattern of response to infection with the HSV IE regulation-deficient mutants tsK and tsB7: stimulation of IFN synthesis occurred in the absence of a functional HSV IE175 (or ICP4) gene product, but did not occur in the absence of uncoating of virus capsids. Cycloheximide treatment (without virus infection) also gave a rapid 30-fold increase in steady-state levels of correctly initiated mRNA from both types of IE94-IFN hybrid genes, but had no effect on cells containing the IE175-IFN construct. Therefore, we conclude that the use of the IE94-IFN constructs identifies a novel HSV regulatory response that requires a previously unrecognized function of HSV and does not involve either IE175 or the pre-IE "virion factor" trans-activators that are known to stimulate transcription of HSV IE and DE genes, respectively.
L2 ANSWER 15 OF 47 MEDLINE

AU Weston K
TI An enhancer element in the short unique region of human cytomegalovirus regulates the production of a group of abundant immediate early transcripts.
SO Virology, (1988 Feb) 162 (2) 406-16.
Journal code: XEA. ISSN: 0042-6822.
AB A 275-bp sequence in the short unique region of human ***cytomegalovirus*** (HCMV) strain AD169 contains a series of five imperfect 18-bp repeats with homology to the SV40 and HCMV major ***immediate*** early enhancers. Plasmids containing these putative HCMV enhancer sequences linked to the human beta-globin gene were transiently transfected into HeLa cells, and the ability of the HCMV sequences to activate beta-globin transcription was assayed. The repeat-containing region stimulated transcription in a position- and orientation-independent manner, to approximately the same degree as that of the SV40 enhancer. A promoter located immediately 3' to the enhancer in the HCMV genome is active only in the presence of the enhancer sequences. Transcription from this HCMV promoter was analysed by a combination of S1 nuclease protection mapping and Northern blotting. At ***immediate*** early times postinfection, at least four extremely abundant differentially ***spliced*** mRNAs were detected; these RNAs constitute a previously unknown class of ***immediate*** early transcript.
L2 ANSWER 18 OF 47 MEDLINE
AU Ramirez-Solis R; Resendez-Perez D; Alvidrez-Quihui L E; Rincon-Limas D E; Varela-Martinez R; Martinez-Rodriguez H G; Barrera-Saldana H A TI New vectors for the efficient expression of mammalian genes in cultured cells.
SO Gene, (1990 Mar 15) 87 (2) 291-4.
Journal code: FOP. ISSN: 0378-1119.
AB We have constructed a new pair of plasmid vectors for the efficient expression of mammalian genes. The first of the new plasmids, pAVE1, was derived from pCMVcat [Foecking and Hofstetter, Gene 45 (1986) 101-105] by replacing the chloramphenicol acetyltransferase-encoding sequences in the latter for a multiple cloning site. Since it possesses the powerful enhancer-promoter unit of the ***immediate*** early gene of human ***cytomegalovirus*** , pAVE1 is ideal for the expression of mammalian genes. The second expression vector, pAVE2, resulted when the 3'-end flanking region from the human growth hormone-encoding gene (hGH) was incorporated in pAVE1. This region provides sequences for 3'-end processing and polyadenylation of primary transcripts. Thus, pAVE2 is suitable for expression of cDNAs in cultured cells, where ***introns*** have little effect on gene expression. To test our new vectors, we inserted the structural region of the chromosomal hGH gene into pAVE1, and its cDNA into pAVE2. By independently transfecting the resulting recombinant plasmids into COS-7 cells, we have achieved high levels of hGH transient expression with both vectors.
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ENTRY SESSION FULL ESTIMATED COST 5.44 5.68

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=> s 935/36/cclst
L1 66 935/36/CCLST

=> s intron?
L2 903 INTRON?

=> s l1 and l2
L3 31 L1 AND L2

=> d kwic

US PAT NO: 5,409,823 [IMAGE AVAILABLE] L3: 1 of 31 US-CL-CURRENT: 435/172.3; 47/DIG.1; 435/172.1; 536/24.1; 800/205; 935/35, **36**, 64

DRAWING DESC:

DRWD(11)

The . . . et al., (1991) Plant Molecular Biology, 17:229-234); plant translational consensus sequences (Joshi, C. P., (1987), Nucleic Acids Research, 15:6643- 6653), **introns** (Luehrsen and Walbot, (1991), Mol. Gen. Genet., 225:81-93) and the like, operably linked to the nucleotide sequence of the transactivator.

DRAWING DESC:

DRWD(24)

To . . . sequence (Joshi, C. P. (1987) Nucleic Acids Research 15:6643-6653) may be also included, as well as plant termination signals and **introns**.

DETDESC:

DETD(53)
. . .
TABLE II
Transient expression experiment using GAL4/VP16 transactivation

| | Specific GUS Activity (nm MU/.mu.g protein) | Fold increase over pLP4 |
|---|---|---|
| pLP4 GAL4 binding site/minimal 35S promoter/GUS pGAL4/VP1 35S promoter/Adh1 **intron**/GAL4/VP16 | | |
| no DNA | 0.02 .+-.. . . | |

=> d kwic 31

US PAT NO: 4,579,821 [IMAGE AVAILABLE] L3: 31 of 31 US-CL-CURRENT: 435/172.3, 69.7, 194, 320.1; 536/23.4, 24.1; 935/6, 34, **36**, 53, 70, 111

DETDESC:

DETD(5)

Durnam, . . . the Eco RI site of the plasmid. The MT-I gene spans about 1.1 kb pairs and contains at least two **introns**.

DETDESC:

DETD(6)

As . . . narrow box, and MT-I gene sequences by a wide box. mRNA coding regions are represented by closed boxes; non-transcribed and **intron** regions are shown by open boxes. Hatched boxes inside the circles represent regions of these genes that were used as. . .
=> d kwic 28-30

US PAT NO: 4,904,582 [IMAGE AVAILABLE] L3: 28 of 31 US-CL-CURRENT: 435/6; 424/44; 435/172.3, 240.2, 243; 436/501; 536/24.1, 24.3, 24.31, 24.32; 935/2, 4, 33, 34, **36**, 77, 78
SUMMARY:

BSUM(47)

The . . . sequences, mitochondrial sequences, plastid sequences, etc. The sequences may involve open reading frames for coding proteins, ribosomal RNA, snRNA, hnRNA, **introns**, untranslated 5'- and 3'-sequences flanking open reading frames, etc. The subject sequences may therefore be involved in inhibiting the availability.
. .
SUMMARY:

BSUM(50)

The . . . involved with metabolic processes, in the formation of amino acids, nucleic acids, or the like, DHFR, etc. as well as **introns** or flanking sequences associated with the open reading frames.

US PAT NO: 4,738,931 [IMAGE AVAILABLE] L3: 29 of 31 US-CL-CURRENT: 435/320.1, 69.51, 91.41, 91.53, 172.1, 172.3, 240.2, 811; 536/23.52; 935/11, 29, 34, **36**, 41

DETDESC:

DETD(28)

It has been revealed that intervening sequences, **introns**, present in the gene of many eucaryotic cells are absent in the human
interferon-.beta. gene. The absence of intervening sequences. . .
US PAT NO: 4,663,281 [IMAGE AVAILABLE] L3: 30 of 31 US-CL-CURRENT: 435/69.1, 69.4, 69.6, 172.3, 240.26, 240.27; 536/23.1, 24.1; 935/34, **36**

DRAWING DESC:

DRWD(5)

FIG. . . . plasmid was constructed from plasmid pSV-.gamma.2bVC (shown in FIG. 1) by removing two Xba I fragments from the .gamma.2b gene **intron** (from the X.sub.2 to the X.sub.4 sites in FIG. 1). Derivatives of plasmid pSV-.gamma.2b.DELTA.X.sub.2/4, labeled A through D, contain inserts. . .

DRAWING DESC:

DRWD(11)

FIG. 10 is an illustration of the nuclectide sequences of DNA comprising an enhancer element located on a major **intron** of a .gamma.2b heavy chain murine gene (X.sub.2/3 fragment).

DETDESC:

DETD(5)

DNA . . . and other regulatory sequences. The enhancer is operative whether located upstream or downstream from the transcription unit or in an **intron**, provided it is within the active region. However, the level of enhancement may vary somewhat depending on its position relative. . .

DETDESC:

DETD(24)

The . . . with respect to the direction of transcription. In order to test whether the putative enhancer sequences located in the major **intron** of the .gamma.2b gene and present in the pSV-.gamma.2b3'R.DELTA.1 deletion plasmids behave similarly, a plasmid with most of the **intron** sequences deleted was constructed. A 1 kb Xba I fragment (X.sub.2/3, see nucleotide sequence, FIG. 10) containing those **intron** sequences with potential enhancer activity were then inserted into either of two sites and in either of the two orientations.. . . The first corresponds to the original position of this fragment in the parental plasmid (as part of the VDJ-C .gamma.2b **intron**) and the second is approximately 1.4 kb upstream (on the 5' side of the V gene segment). Four plasmids were. . .

DETDESC:

DETD(26)

Cell . . . the expression of .gamma.2b heavy chain. As indicated in FIG. 5, cells transfected with plasmid pSV-.gamma.2b.DELTA.X.sub.2/4 (with most of the **intron** deleted) did not synthesize significant levels of .gamma.2b protein (lanes 3 and 4). The insertion of the X.sub.2/3 fragment containing the enhancer into the **intron** site (the normal position of this fragment) restored the expression of .gamma.2b protein in both the normal (FIG. 5, lanes. . .

DETDESC:

DETD(27)

These results clearly demonstrate that the **intron** sequences deleted in the 3'R.DELTA.2 mutant plasmid

have a direct effect on transcription in a manner that is analogous to. . .

DETDESC:

DETD(45)

The . . . enhancing activity. The BstXI to EcoRI fragment (XR), containing the first E.sub..beta. gene exon and a portion of the first **intron**, had no detectable enhancer activity. Two short sequences upstream of the promoter had been identified as conserved elements when compared. . .

CLAIMS:

CLMS(16)

16. . . . claim 10 wherein said enhancer element, when present as part of the endogenous genome of a lymophoid cell in an **intron** of a .gamma.2b heavy chain gene, serves to enhance production of a .gamma.2b heavy chain protein.

=> d kwic 20-27

US PAT NO: 5,070,010 [IMAGE AVAILABLE] L3: 20 of 31 US-CL-CURRENT: 435/6, 5, 69.1, 172.3; 436/501; 935/6, 10, 29, **36**, 77, 78, 88

DETDESC:

DETD(30)

To . . . the Rous sarcoma virus long terminal repeat transcription control region, and the genomic rat preproinsulin gene. The latter contributes an **intron** and an efficient polyadenylation signal.

US PAT NO: 5,057,422 [IMAGE AVAILABLE] L3: 21 of 31 US-CL-CURRENT: 435/240.4, 69.1, 70.1, 172.3, 252.3, 320.1; 536/24.1; 800/205; 935/35, **36**, 64

SUMMARY:

BSUM(17)

The . . . cases be still without consequences for the expression and function of the protein. The place, length and nucleotide sequence of **introns** can generally be varied as well, provided they can be processed by the host.

US PAT NO: 5,034,322 [IMAGE AVAILABLE] L3: 22 of 31 US-CL-CURRENT: 435/172.3, 69.1, 183, 252.2, 252.3, 252.33, 320.1; 536/23.2, 23.7; 935/30, 35, **36**, 67

SUMMARY:

BSUM(53)

The . . . bacterial or mammalian protein. The structural sequence includes a start codon and a stop codon. The structural sequence may contain **introns** which are removed from the mRNA prior to translation.

DETDESC:

DETD(119)

A structural sequence may contain **introns** and exons; such a structural sequence may be derived from DNA, or from an mRNA primary transcript. Alternately, a structural sequence may be derived from processed mRNA, from which one or more **introns** have been deleted.
US PAT NO: 5,017,478 [IMAGE AVAILABLE] L3: 23 of 31 US-CL-CURRENT: 435/69.1, 70.1, 172.3, 212, 240.2, 254.2, 320.1; 536/23.2, 23.4, 23.51; 935/27, 33, **36**, 60, 65, 69, 70
SUMMARY:

BSUM(15)

Preferred . . . non-selectable gene encodes tissue plasminogen activator of the human variety. The desired genes encoding t-PA can optionally, but preferrably, contain **introns** such as a cDNA/genomic hybrid gene. Preferred t-PA expression vectors are pPA003, pPA509, and pPA202.

DRAWING DESC:

DRWD(4)

a. The DNA sequence of the amino terminal region of the t-PA gene extending from **intron** A through the coding region and
5'--untranslated region to **intron** A'. The dashed line shows the structure and sequence of the amino terminal region of the t-PA chromosomal gene as. . .

DRAWING DESC:

DRWD(5)

b. The Nar I fragment of pPA103 extending from **intron** A to a Nar I site in t-PA cDNA was inserted into pPA104. This allowed removal of a 3.3 Kb. . .

DETDESC:

DETD(34)

The structural gene may be essentially any DNA sequence (e.g., cDNA or genomic clone with **introns**) that upon expression codes for a desired polypeptide, including heterologous proteins or endogenous proteins or proteins naturally produced by the. . .

DETDESC:

DETD(82)

The . . . a portion of the 5' untranslated sequences, and 105 nucleotides encoding the pre- and pro- peptides, separated by a large **intron** (FIG. 2a).

DETDESC:

DETD(84)

The . . . into the unique Bgl II site of pneo5 thus generating pPA003. Because the t-PA coding region contains both genomic (including **introns** and exons) and cDNA sequences, this gene construct is referred to as a hybrid t-PA gene.

DETDESC:

DETD(85)

This . . . contains the 5' end of the gene including the 5' untranslated sequences of t-PA, the pre- and pro-coding regions, the **intron** between these regions, and the coding region for mature t-PA.
US PAT NO: 4,988,624 [IMAGE AVAILABLE] L3: 24 of 31 US-CL-CURRENT: 435/320.1, 172.3; 536/23.2, 23.5, 23.51, 24.1; 935/27, **36**

SUMMARY:

BSUM(8)

It . . . matured mRNA is referred to as the "exon" while the separating sequence is referred to as the "intervening sequence" or "**intron**". Although the biological roles or functions of the **introns** remains still almost unknown, it is known that a gene without the **intron** such as those coding ovalbumin [Wickens, M. P. et al. (1980), Nature, Vol. 285, P628] or viral protein [Lai, C-J.. . . Proc. Natl. Acad. Sci. USA, Vol. 76, P71] produces far less protein in the animal cell as compared with the **intron** containing gene. It is also known that accumulation of stable mRNA occurs when the **intron** from .beta.-globin gene is added to SV40 gene devoid of the **intron** [Hamer, D. H. et al. (1979), Cell, Vol. 18, P1299].

SUMMARY:

BSUM(9)

Removal of the sequence corresponding to the **intron** from nascent mRNA, which is transcribed from gene, is referred to as the "splicing". The splicing is presumed to be. . .

SUMMARY:

BSUM(11)

Therefore, the correct splicing is required in order to produce LT by introducing LT gene with the **intron** into the cultured animal cell. The present inventors have found that normal splicing occurs to secrete LT into the culture. . .

SUMMARY:

BSUM(13)

In . . . communications in molecular biology, Cold Spring Harbor Laboratory (1983)]. It is also known that the enhancer is present in the **intron** of immunoglobulin gene [ibid].

DETDESC:

DETD(65)

LT gene consists of at least four exons and three **introns**. 1st Exon includes TATAbox-like sequence (TATAAA) which is normally found in the eucaryote promoter region. 2nd Exon includes initiation codon. . .
CLAIMS:

CLMS(1)

What . . . is:

1. A recombinant DNA sequence which codes for human lymphotoxin and contains the genomic DNA sequence for lymphotoxin, including **introns**.
CLAIMS:

CLMS(2)

2. A lymphotoxin expression vector comprising a DNA sequence containing the genomic DNA sequence, including **introns**, for human lymphotoxin operably linked to a promoter selected from the group consisting of an early promoter of SV40, a. . .

CLAIMS:

CLMS(5)

5. A lymphotoxin expression vector comprising a DNA sequence wherein a DNA sequence containing the genomic DNA sequence, including **introns**, for human lymphotoxin operably linked to the human lymphotoxin promoter region, and an enhancer sequence of Rous sarcoma virus which. . .
US PAT NO: 4,943,527 [IMAGE AVAILABLE] L3: 25 of 31 US-CL-CURRENT: 435/69.6, 72, 172.3, 320.1; 935/11, 34, **36**, 60, 70
DETDESC:

DETD(11)

A . . . 3' untranslated regions. A comparison of the genomic and cDNA sequences revealed the presence in the genomic gene of three **introns** which interrupt the coding sequence in (a) the 5' untranslated region, (b) an 18 amino acid signal sequence, and (c). . .

DETDESC:

DETD(14)

Vectors . . . used in the vectors designed for production of complete apolipoproteins, to avoid limitations in bacterial and yeast systems in transcribing **intron**-containing genomic genes. The gene in the yeast vector contained codons for the mature apoAI minus the first seven N-terminal codons.

DETDESC:

DETD(15)

A . . . as divalent zinc and iron. Studies performed in support of the present application and other co-owned

applications indicate that genomic (**intron**-containing) genes, and cDNA copies thereof, encoding a variety of protein and protein segments, including apolipoproteins and apolipoprotein .alpha.-helical segments, are. . .

DETDESC:

DETD(111)

To . . . gel purification. The PstI fragment extends from a point in the 5' untranslated region through the entire coding sequence (with **introns**) and terminates beyond the poly A addition site. The purified fragment was blunt ended by digesting away the single-stranded 3'. . .

US PAT NO: 4,935,349 [IMAGE AVAILABLE] L3: 26 of 31 US-CL-CURRENT: 435/69.5, 69.6, 171, 172.3, 212, 254.3, 320.1, 913, 917; 530/351, 388.1, 866, 867; 536/23.51, 23.53, 24.1; 935/6, 10, 24, 34, **36**, 48, 60, 68

DRAWING DESC:

DRWD(2)

FIG. . . . acid sequence of a portion of the A. nidulans tpiA genomic clone. Slash marks (/) in the nucleotide sequence indicate exon-**intron** boundaries.

DRAWING DESC:

DRWD(6)

FIG. . . . illustrates the nucleotide sequence and translated amino acid sequence of the A. niger adh A gene. Slash marks (/) indicate exon-**intron** boundaries.

DRAWING DESC:

DRWD(9)

FIG. 8 illustrates the nucleotide sequence and translated amino acid sequence of the A. niger tpi A gene. Slash marks indicate exon-**intron** boundaries.

US PAT NO: 4,920,211 [IMAGE AVAILABLE] L3: 27 of 31 US-CL-CURRENT: 435/320.1, 69.1, 172.3; 536/23.1, 24.1; 935/27, 32, 34, **36**, 57

DETDESC:

DETD(14)

The . . . the more familiar subgroup C adenoviruses Ad2 and Ad5. The early E1A gene transcripts differ only by the length of **intron** removed. Their translation products share common amino- and carboxy-terminal peptide sequences. The defective mutant Ad3 hr15 has two short tandem. . .

DETDESC:

DETD(29)

Bacteriophage-mediated . . . would require cloning of the cDNA frms of the E1A genes since bacterial cells lack the capacity for removal of **introns**. The cDNA would be synthesized using standard procedures with mRNA isolated from Ad 3 hr 15 revertant infected cells (recall that Ad 3 hr 15-dl 7 generates abundant E1A m RNA early and throughout infection). The 13S (small **intron**) mRNA would be the cDNA form of choice if products capable of transactivation are desired. Cloning of the cDNA into. . .

=> d kwic 10-19

US PAT NO: 5,220,007 [IMAGE AVAILABLE] L3: 10 of 31 US-CL-CURRENT: 536/23.1, 22.1, 23.5, 25.1; 935/2, 8, **36**
DETDESC:

DETD(28)

A . . . SP6 RNA polymerase transcription of a HindIII-linearized pGem-2 clone, pT7H.beta..DELTA.6. 514 RNA is antisense to the first two exons and **intron** of human .beta.-globin pre-mRNA and was chosen for the reasons described below. 514 RNA labeled with a
[.alpha..about..sup.32 P]GTP, [.alpha..about..sup.32. . .
DETDESC:

DETD(34)

For . . . which is 514 nucleotides long (termed 514 RNA) was used. 514 RNA is antisense to the first two exons and **intron** of human .beta.-globin pre-mRNA. The underlying reasoning was that, because it is antisense to a pre-mRNA, 514 RNA would not. . .

US PAT NO: 5,217,864 [IMAGE AVAILABLE] L3: 11 of 31 US-CL-CURRENT: 435/6, 7.8, 68.1, 70.1; **935/36**

DETDESC:

DETD(17)

A . . . construct where the coding sequence itself is not found in nature (e.g., a cDNA where the genomic coding sequence contains **introns**, or synthetic sequences having codons different than the native gene). Allelic variations or naturally-occurring mutational events do not give rise. . .

US PAT NO: 5,196,525 [IMAGE AVAILABLE] L3: 12 of 31 US-CL-CURRENT: 536/24.1; 435/69.1, 70.1, 172.3, 320.1; 800/205; 935/30, 35, **36**

DETDESC:

DETD(22)

2. . . . the natural gene (plant, animal, bacterial, viral, and fungal) which encode the primary RNA product, i.e., consisting of exons and **introns**, e.g., natural Polymerase II and Polymerase III transcribed genes of eukaryotes.

US PAT NO: 5,196,329 [IMAGE AVAILABLE] L3: 13 of 31 US-CL-CURRENT: 435/172.3, 320.1; 536/24.1; 935/35, **36**, 67

DETDESC:

DETD(7)

A . . . one or more nucleotides. The structural gene may constitute an uninterrupted coding sequence or it may include one or more **introns**, bounded by the appropriate plant functional splice junctions. The structural gene may be a composite of segments derived from a. . .

DETDESC:

DETD(28)

A . . . reading frame, a requirement well understood in the art. An exception to this requirement exists in the case where an **intron** separates the coding sequence derived from one gene from the coding sequence of the other. In that case, the coding sequences must be bounded by compatible splice sites, and the **intron** splice sites must be positioned so that the correct reading frame for both genes is established in the fusion after the **introns** are removed by post-transcriptional processing. Differences in rates of expression or developmental control may be observed when a given gene. . .
US PAT NO: 5,187,267 [IMAGE AVAILABLE] L3: 14 of 31 US-CL-CURRENT: 536/23.1; 47/58; 435/172.3, 240.4; 536/23.6, 24.1; 800/205, DIG.40, DIG.44; 935/35, **36**, 67
DRAWING DESC:

DRWD(7)

FIG. . . . and Sall ("S"). The hatched shading indicates promoter region, the black shading represents coding region, and the white boxes represent **introns**. The "." symbols are representative of scaffold attachment regions (SAR) found in those sequences. The number assigned to each fragment. . .

DETDESC:

DETD(8)

Tomato hsp80 is characterized by having a mRNA of about 2.3 kb, two **introns**, a predicted pl of about 4.69, and a molecular weight of 80,479.8 daltons. In the direction of transcription, the first **intron** is approximately 995 bp in length and the second is approximately 109 bp in length. The polypeptides encoded by tomato. . .

DETDESC:

DETD(27)

The . . . than about 10 kbp, frequently being less than about 2 kbp, and may include all or a portion of an **intron** (including the splice sites). The 5'-non-coding region which is employed will be proximal to (usually within 20 bp) or abut. . .

DETDESC:

DETD(33)

In . . . to provide an expression cassette having a 5' non-coding region capable of initiating transcription and

one or more of either **introns** or a 3' non-coding termination region, which are obtainable from tomato hsp80.

DETDESC:

DETD(37)

Scaffold . . . the insertion of one or more scaffold attachment regions into the coding region of the DNA sequence of interest in **intron** or exon sequences. In another preferred embodiment, one or more scaffold attachment regions are positioned flanking an expression cassette of. . .

DETDESC:

DETD(67)

A . . . with 7100 cDNA, and several clones are isolated. One of these clones, Ghsp4, was sequenced by methods described above. Two **introns** one 995 bp in length and the other 109 bp in length, are found in genomic clone Ghsp4. FIG. 2. To determine whether any **intron** exists in the region covered by cDNAs 7100 and 7115, pairs of primers are used to amplify portions of the. . . Comparison to corresponding PCR reactions from the cDNA indicate that the regions represented by the cDNA 7100 do not contain **introns**, as the PCR products using the cDNAs as template are identical in size to PCR products using genomic DNA as. . .

US PAT NO: 5,182,200 [IMAGE AVAILABLE] L3: 15 of 31 US-CL-CURRENT: 435/172.3, 69.1, 70.1, 240.4, 252.2, 252.3, 252.33; 536/23.2, 23.6, 24.1; 935/35, **36**, 41, 67
SUMMARY:

BSUM(4)

Following . . . heterologous foreign structural genes. N. Murai et al. (1983) Science 222:476-482, reported the ocs promoter could drive expression of an **intron**-containing fusion gene having foreign coding sequences. (Manipulations of the TIP Plasmids). R. F. Barker et al. (1983) Plant Molec. Biol.. . .

SUMMARY:

BSUM(25)

The . . . of the T.sub.L region of pTiAch5 (J. Gielen et al. (1984) EMBO J. 3:835-846). Published T-DNA genes do not contain **introns** and do have sequences that resemble canonical eukaryotic promoter elements and polyadenylation sites.

SUMMARY:

BSUM(39)

N. . . . structural gene to a phaseolin structural gene. The encoded fusion protein was produced under control of the T-DNA promoter. Phaseolin-derived **introns** underwent proper post-transcriptional processing.

DETDESC:

DETD(12)

As . . . of the expression product. The structural gene may constitute an uninterrupted coding sequence or it may include one or more **introns**, bounded by the appropriate plant functional splice junctions, which may be obtained from synthetic or a naturally occurring source. The. . .

DETDESC:

DETD(19)

A . . . structural requirement which is well understood in the art. An exception to this requirement exists in the case where an **intron** separates coding sequences derived from a foreign structural gene from the coding sequences of the pRi T.sub.L -DNA structural gene. In that case, both structural genes must be provided with compatible splice sites, and the **intron** splice sites must be so positioned that the correct reading frame for the pRi T.sub.L -DNA promoterposition donated structural gene and the foreign structural gene are restored in phase after the **intron** is removed by post-transcriptional processing. Differences in rates of expression or developmental control may be observed when a given foreign. . .

DETDESC:

DETD(48)

Though to date no **introns** have been found in any of the fourteen sequenced pTi T-DNA genes, (R. F. Barker et al. (1983) Plant Mol. Biol. 2:335-350), J. Gielen et al. (1984) EMBO J. 3:835-846), **introns** are present in some plant nuclear genes; pRi T.sub.L -DNA genes could have **introns**. Transcript mapping (Example 1.9) did not generally indicate spliced mRNA. However, analysis of mRNA encoded between positions 6500 and 9000. . . as found. The coding region of ORF 8 was scanned for sequences which matched consensus donor (5'exon. . . ##STR2## **intron3**', the "*" indicating the splice site) and acceptor (**intron**. . . ##STR3## exon) **intron** splice sequences and conformed to the G-T/A-G rule (R. Breathnach et al. (1978) Proc. Natl. Acad. Sci. USA 75:4853-4857) and. . . of 724, 758, 943, 1270, or 1325 bp, respectively, which is in the size range observed. Proper processing of an **intron**-containing genes in T-DNA has been observed (e.g. N. Murai et al. (1983) Science 222:476-482).

DETDESC:

DETD(93)

This . . . encodes a protein toxic to insect larvae. Phaseolin, lectin, and thaumatin are eukaryotic genes; crystal protein is prokaryotic. Phaseolin contains **introns**; lectin and crystal protein do not. The lectin gene itself contains no **introns** and could be obtained on a 5.7 kbp HindIII fragment from a genomic clone (L. M. Hoffman (1984) J. Mol.. . .

US PAT NO: 5,177,307 [IMAGE AVAILABLE] L3: 16 of 31 US-CL-CURRENT: 800/205; 423/437M; 435/69.1, 70.1, 172.3, 183, 240.4, 320.1; 536/23.6, 24.1; 800/DIG.44; 935/35, **36**, 64, 67

DRAWING DESC:

DRWD(4)

FIGS. . . . that region. The start of the pZ130 gene transcript is indicated by the underlined, boldfaced (A) at

position 2567. An **intron** in the gene sequences is indicated by the lower case sequence from position 2702 through position 2921. Sites for common. . .
DETDESC:

DETD(7)

To . . . an enzyme in a cytokinin metabolic pathway, and a transcriptional and translational termination region functional in plants. One or more **introns** may also be present. The DNA sequence may have any open reading frame encoding an enzyme involved in cytokinin metabolism, or a sequence complementary to a genomic sequence, where the sequence may be an open reading frame, an **intron**, a non-coding leader sequence, or any other sequence where the complementary sequence will inhibit transcription, messenger RNA processing, e.g. splicing,. . .
DETDESC:

DETD(151)

pCGN1273 . . . fragment of DNA (base number 566 to 1055) from a PG genomic clone which spans the 5' end of the **intron**/exon junction. This fragment was cloned into the XbaI site resulting in plasmid pCGN1215. pCGN1215 was linearized at the unique BglII. . .
DETDESC:

DETD(155)

The 0.5 Kb fragment of the PG genomic clone spanning the **intron**/exon junction was cloned into pCGN1267 at the ClaI site in an antisense direction yielding plasmid pCGN1225. This plasmid was linearized. .
.
DETDESC:

DETD(179)

The . . . of Bluescript (+) (Stratagene) resulting in pCGN1288. This clone contains sequences from the EcoRI site at position 1651 in the **intron** of the 2All gene to the EcoRI site located 2.5 Kb upstream of the XhoI site at position 1 of. . .

US PAT NO: 5,175,095 [IMAGE AVAILABLE] L3: 17 of 31 US-CL-CURRENT: 435/69.1, 70.1, 172.3, 240.4, 320.1; 536/24.1; 800/205, DIG.44; 935/35, **36**, 64, 67

DRAWING DESC:

DRWD(3)

FIGS. . . . that region. The start of the pZ130 gene transcript is indicated by the underlined, boldfaced "A" at position 2567. An **intron** in the gene sequence is indicated by the lower case sequence from position 2702 through position 2921. Sites for common. . .
DETDESC:

DETD(5)

A . . . for the transcription and translation of a DNA sequence of interest it is considered an expression cassette. One or more **introns** may be also be present. For use in the subject invention, transcriptional

initiation regions which are expressible in ovary tissue. . .
DETDESC:

DETD(17)

The . . . enzyme, or a sequence complementary to a genomic sequence, where the genomic sequence may be an open reading frame, an **intron**, a noncoding leader sequence, or any other sequence where the complementary sequence inhibits transcription, messenger RNA processing, for example, splicing,. . .

US PAT NO: 5,149,785 [IMAGE AVAILABLE] L3: 18 of 31 US-CL-CURRENT: 530/350, 397; 930/25; **935/36**

DETDESC:

DETD(17)

Any . . . A Practical Approach, MRL Press, Ltd., Oxford, U.K., Vol. I, II.) Clones derived from genomic DNA may contain regulatory and **intron** DNA regions in addition to coding regions; clones derived from cDNA will contain only exon sequences. Whatever the source, the. . .
US PAT NO: 5,070,192 [IMAGE AVAILABLE] L3: 19 of 31 US-CL-CURRENT: 435/7.4, 7.1, 172.3, 233; 436/501, 536, 543, 811, 815; 530/389.1; 536/23.2; 935/12, 14, 29, **36**, 81, 88
SUMMARY:

BSUM(18)

In . . . of producing eukaryotic topoisomerase I polypeptide is presented which comprises providing a host cell which can replicate and express an **intron**-free DNA sequence of eukaryotic topoisomerase I polypeptide, growing the host cell, and recovering the eukaryotic topoisomerase I polypeptide. Also contemplated. . .

DETDESC:

DETD(18)

The . . . also such eukaryotes as yeast, filamentous fungi, as well as plant and animal cells which can replicate and express an **intron**-free DNA sequence of eukaryotic topoisomerase I. However, prokaryotes are preferred as the host organism.

CLAIMS:

CLMS(9)

9. . . . least one epitope for autoantibodies to eukaryotic topoisomerase I comprising:
(a) providing a host cell which replicates and expresses an **intron**-free DNA sequence of human topoisomerase I polypeptide; (b) growing said host cell; and
(c) recovering said human topoisomerase I polypeptide.

=>
=> log y

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=> d ti 1-20

L2 ANSWER 1 OF 7704 MEDLINE
TI Detection of the human T cell lymphoma virus p19 in cells of some patients with cutaneous T cell lymphoma and leukemia using a monoclonal antibody.

L2 ANSWER 2 OF 7704 MEDLINE
TI Regulation of human T-cell proliferation: T-cell growth factor and isolation of a new class of type-C retroviruses from human T-cells.
L2 ANSWER 3 OF 7704 MEDLINE
TI Isolation of a new type C retrovirus (HTLV) in primary uncultured cells of a patient with Sezary T-cell leukaemia.
L2 ANSWER 4 OF 7704 MEDLINE
TI Growth of human normal and leukemic T cells: T-cell growth factor (TCGF) and the isolation of a new class of RNA tumor viruses ( HTLV).

L2 ANSWER 5 OF 7704 MEDLINE
TI Characterization of the reverse transcriptase from a new retrovirus (HTLV) produced by a human cutaneous T-cell lymphoma cell line.

L2 ANSWER 6 OF 7704 MEDLINE
TI Immunological properties of a type C retrovirus isolated from cultured human T-lymphoma cells and comparison to other mammalian retroviruses.

L2 ANSWER 7 OF 7704 MEDLINE
TI Characterization and distribution of nucleic acid sequences of a novel type C retrovirus isolated from neoplastic human T lymphocytes.

L2 ANSWER 8 OF 7704 MEDLINE
TI Human T cell leukemia-lymphoma virus: characterization, biology and significance.

L2 ANSWER 9 OF 7704 MEDLINE
TI Natural antibodies to human retrovirus HTLV in a cluster of Japanese patients with adult T cell leukemia.

L2 ANSWER 10 OF 7704 MEDLINE
TI Human T cell hybridomas secreting immune interferon.
L2 ANSWER 11 OF 7704 MEDLINE
TI Identification of HTLV p19 specific natural human antibodies by competition with monoclonal antibody.

L2 ANSWER 12 OF 7704 MEDLINE
TI Human T-cell leukemia-lymphoma virus (HTLV) is in T but not B lymphocytes from a patient with cutaneous T-cell lymphoma.

L2 ANSWER 13 OF 7704 MEDLINE
TI The human type-C retrovirus, HTLV, in Blacks from the Caribbean region, and relationship to adult T-cell leukemia/lymphoma. {

L2 ANSWER 14 OF 7704 MEDLINE
TI A new subtype of human T-cell leukemia virus (HTLV-II) associated with a T-cell variant of hairy cell leukemia.
L2 ANSWER 15 OF 7704 MEDLINE
TI Expression of cellular homologues of retroviral onc genes in human hematopoietic cells.

L2 ANSWER 16 OF 7704 MEDLINE
TI HTLV: the virus of adult T-cell leukaemia in Japan and elsewhere [letter].

L2 ANSWER 17 OF 7704 MEDLINE
TI Common site of integration of HTLV in cells of three patients with mature T-cell leukaemia-lymphoma: a retraction [retraction of Hahn B, Manzari V, Colombini S, Franchini G, Gallo RC, Wong-Staal F. In: Nature 1983 May 19-25;303(5914):253-6].
L2 ANSWER 18 OF 7704 MEDLINE
TI Cutaneous T-cell lymphoma: a review.

L2 ANSWER 19 OF 7704 MEDLINE
TI Unusual virus produced by cultured cells from a patient with AIDS.
L2 ANSWER 20 OF 7704 MEDLINE
TI Origin of adult T-cell leukemia virus. Implication for its zoonosis.
=> d 7 au,ti,so,py,ab

L2 ANSWER 7 OF 7704 MEDLINE
AU Reitz M S Jr; Poiesz B J; Ruscetti F W; Gallo R C
TI Characterization and distribution of nucleic acid sequences of a novel type C retrovirus isolated from neoplastic human T lymphocytes.
SO Proc Natl Acad Sci U S A, (1981 Mar) 78 (3) 1887-91. Journal code: PV3. ISSN: 0027-8424.
PY 1981
AB A type C retrovirus (designated HTLV) recently isolated from a cell line derived from a lymph node and later from peripheral blood of a person with cutaneous T-cell lymphoma (mycosis fungoides) was characterized by nucleic acid hybridization experiments. HTLV [3H]cDNA hybridized 90% to its own 70S RNA with kinetics consistent with the genetic complexity of other retroviruses, but it did not hybridize substantially to RNA or proviral DNA from any animal retroviruses (types B, C, and D), including those from nonhuman primates. Conversely, [3H]cDNA from other retroviruses did not

hybridize to RNA or DNA of the human T-cell line producing HTLV. HTLV proviral sequences were present (two to three copies per haploid genome) in DNA of these cells, and homologous sequences were present in the cell cytoplasmic RNA (0.3% viral sequences by weight). HTLV -related nucleic acid sequences were not found in DNA from various other human tissues. The results indicate that HTLV is a new class of type C virus that is not an endogenous (genetically transmitted) retrovirus in man.

=> d ti 21-40

L2 ANSWER 21 OF 7704 MEDLINE
TI Isolation of a new retrovirus in a patient at risk for acquired immunodeficiency syndrome.

L2 ANSWER 22 OF 7704 MEDLINE
TI Retroviruses in human leukemia.

L2 ANSWER 23 OF 7704 MEDLINE
TI Human tumor viruses. RNA tumor viruses.

L2 ANSWER 24 OF 7704 MEDLINE
TI Characteristic clinical features of adult T-cell leukemia in Sado Island.

L2 ANSWER 25 OF 7704 MEDLINE
TI Interleukins and immunosuppressive factors: a regulatory system?.

L2 ANSWER 26 OF 7704 MEDLINE
TI Human T-cell leukemia-lymphoma virus (HTLV).

L2 ANSWER 27 OF 7704 MEDLINE
TI Identification of envelope glycoprotein encoded by env gene of human T-cell leukemia virus.

L2 ANSWER 28 OF 7704 MEDLINE
TI Human leukemia virus associated with adult T-cell leukemia.

L2 ANSWER 29 OF 7704 MEDLINE
TI [Study of virus-associated lymphomas in primates using a model of malignant lymphoma of the baboon].
Izuchenie virusassotsiirovannykh gemoblastozov primatov na modeli zlokachestvennoi limfomy pavianov.

L2 ANSWER 30 OF 7704 MEDLINE
TI RNA-tumorviruses, oncogenes, and their possible role in human carcinogenesis.

L2 ANSWER 31 OF 7704 MEDLINE
TI [Presence of anti-HTLV (human T-cell leukemia virus) antibodies in blood donors from Martinique].
Presence d'anticorps anti-HTLV (human T-cell leukemia

virus) chez les donneurs de sang de la Martinique.

L2 ANSWER 32 OF 7704 MEDLINE
TI [Etiological aspects of leukemias in primates including man]. Nekotorye aspekty etiologii leikozov primatov, vkliuchaia cheloveka.
L2 ANSWER 33 OF 7704 MEDLINE
TI [AIDS and its association with human tumors and viruses. A viral and/or immunogenetic cause?].
Le SIDA et son association avec des tumeurs et virus humains. Cause virale et/ou immunogenetique?.

L2 ANSWER 34 OF 7704 MEDLINE
TI The science base underlying research on acquired immune deficiency syndrome.

L2 ANSWER 35 OF 7704 MEDLINE
TI [Antibodies against human T-cell leukemia virus (HTLV) in male homosexuals with acquired immunodeficiency syndrome]. Antikorper gegen das Human T-cell Leukemia "Virus (HTLV)". Bei mannlichen Homosexuellen mit erworbenem Immundefekt-Syndrom.
L2 ANSWER 36 OF 7704 MEDLINE
TI [AIDS, acquired immunodeficiency syndrome and its possible link to human T-cell leukemia-lymphoma virus, the retrovirus inducer of T-cell leukemia in the adult].
AIDS, sindrome de inmunodeficiencia adquirida y su posible vinculacion con HTLV, retrovirus inductor de la leucemia T del adulto.

L2 ANSWER 37 OF 7704 MEDLINE
TI No evidence for HTLV infection among leukaemia patients in Germany [letter].

L2 ANSWER 38 OF 7704 MEDLINE
TI Detection of antibodies to adult T-cell leukemia (ATL)-associated virus in ATL patients' sera by immunoelectron microscopy.
L2 ANSWER 39 OF 7704 MEDLINE
TI Adult T-cell lymphoma leukemia in Western countries.
L2 ANSWER 40 OF 7704 MEDLINE
TI Retrovirus terminology [letter].

=> d 41-60 ti

L2 ANSWER 41 OF 7704 MEDLINE {
TI Productive infection and cell-free transmission of human T-cell leukemia virus in a nonlymphoid cell line.

L2 ANSWER 42 OF 7704 MEDLINE
TI Detection of lymphocytes producing a human retrovirus associated with adult T-cell leukemia by syncytia induction

assay.
L2 ANSWER 43 OF 7704 MEDLINE
TI Human T-cell leukemia virus type II transforms normal human lymphocytes.

L2 ANSWER 44 OF 7704 MEDLINE
TI A rapid and sensitive assay for proviral sequences of a human retrovirus (HTLV) in leukemic cells.

L2 ANSWER 45 OF 7704 MEDLINE
TI Budding type C virus particles in a human T cell line derived from acute lymphoblastic leukemia.

L2 ANSWER 46 OF 7704 MEDLINE
TI Pathogenesis of T cell lymphoma of skin.

L2 ANSWER 47 OF 7704 MEDLINE
TI Antibodies against three purified structural proteins of the human type-C retrovirus, HTLV, in Japanese adult T-cell leukemia patients, healthy family members, and unrelated normals.
L2 ANSWER 48 OF 7704 MEDLINE
TI Fulminant human T cell leukaemia lymphoma masquerading as acute viral infection of the nervous system.

L2 ANSWER 49 OF 7704 MEDLINE
TI Retroviruses associated with human leukemias and lymphomas.

L2 ANSWER 50 OF 7704 MEDLINE
TI T cell proliferation and human T cell leukemia virus (HTLV ).

L2 ANSWER 51 OF 7704 MEDLINE
TI Association of human T-cell leukaemia/lymphoma virus with the Tac antigen marker for the human T-cell growth factor receptor.
L2 ANSWER 52 OF 7704 MEDLINE
TI HTLV antibody positivity and incidence of adult T-cell leukaemia in Kochi prefecture, Japan [letter].

L2 ANSWER 53 OF 7704 MEDLINE
TI Origin of human T-cell leukaemia-lymphoma virus [letter].

L2 ANSWER 54 OF 7704 MEDLINE
TI Complete amino acid sequence of human T-cell leukemia virus structural protein p15.

L2 ANSWER 55 OF 7704 MEDLINE
TI The possible etiological role of retroviruses in human tumors.
L2 ANSWER 56 OF 7704 MEDLINE

TI Retroviruses in human tumors.

L2 ANSWER 57 OF 7704 MEDLINE
TI Molecular characterization of genome of a novel human T-cell leukaemia virus.

L2 ANSWER 58 OF 7704 MEDLINE
TI Cell surface antigen expression in newborn cord blood lymphocytes infected with HTLV.

L2 ANSWER 59 OF 7704 MEDLINE
TI Restricted expression of human T-cell leukemia--lymphoma virus ( HTLV) in transformed human umbilical cord blood lymphocytes.

L2 ANSWER 60 OF 7704 MEDLINE
TI Transformation of human umbilical cord blood T cells by human T-cell leukemia/lymphoma virus.

=> d 44,54,au,ti,so,py,ab

L2 ANSWER 44 OF 7704 MEDLINE
AU Manzari V; Agliano A M; Gallo R C; Wong-Staal F
TI A rapid and sensitive assay for proviral sequences of a human retrovirus (HTLV) in leukemic cells.
SO Leuk Res, (1983) 7 (5) 681-6.
Journal code: K9M. ISSN: 0145-2126.
PY 1983
AB Whole cells of cellular DNA from leukemia patients were used in blot hybridization to cloned probes of a human retrovirus HTLV. The results demonstrated the facility of screening large numbers of samples of limited material for the presence of low copy number of HTLV sequences.

L2 ANSWER 54 OF 7704 MEDLINE
AU Copeland T D; Oroszlan S; Kalyanaraman V S; Sarngadharan M G; Gallo R C
TI Complete amino acid sequence of human T-cell leukemia virus structural protein p15.
SO FEBS Lett, (1983 Oct 17) 162 (2) 390-5.
Journal code: EUH. ISSN: 0014-5793.
PY 1983
AB The complete amino acid sequence of human T-cell leukemia virus ( HTLV) structural protein p15 has been determined. The intact protein and peptides generated by enzymatic digestion and acid cleavage were purified by reversed-phase liquid chromatography and subjected to semi-automated Edman degradation. HTLV p15 is a basic linear polypeptide composed of 85 amino acids with Mr 9458. The primary structure indicates that HTLV p15 is homologous to the nucleic acid binding proteins of other type-C { retroviruses and especially related to bovine leukemia virus p12.

=> {d ti 61-80
'{D' IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system. For a list of commands available to you in the current file, enter "HELP COMMANDS" at an arrow prompt (=>).

=> d ti 61-80

L2 ANSWER 61 OF 7704 MEDLINE
TI Homology of human T-cell leukaemia virus envelope gene with class I HLA gene.

L2 ANSWER 62 OF 7704 MEDLINE
TI Cell lines producing human T-cell lymphoma virus show altered HLA expression.

L2 ANSWER 63 OF 7704 MEDLINE
TI Antibodies to human T cell leukaemia virus-associated membrane antigens in haemophiliacs: evidence for infection before 1980.

L2 ANSWER 64 OF 7704 MEDLINE
TI Functional T4 helper cells in patient with HTLV related Sezary syndrome [letter].

L2 ANSWER 65 OF 7704 MEDLINE
TI Generation of an HLA-restricted cytotoxic T cell line reactive against cultured tumor cells from a patient infected with human T cell leukemia/lymphoma virus.

L2 ANSWER 66 OF 7704 MEDLINE
TI Antibodies against human T-cell leukemia/lymphoma virus ( HTLV) and expression of HTLV p19 antigen in relatives of a T-cell leukemia patient originating from Surinam.

L2 ANSWER 67 OF 7704 MEDLINE {
TI Human T-cell leukemia virus type I: induction of syncytia and inhibition by patients' sera.

L2 ANSWER 68 OF 7704 MEDLINE
TI Antibodies to human T-cell leukemia virus membrane antigens ( HTLV-MA) in hemophiliacs.

L2 ANSWER 69 OF 7704 MEDLINE
TI Antibodies to ATLV (HTLV) in Nigerian blood donors and patients with chronic lymphatic leukaemia or lymphoma [letter].

L2 ANSWER 70 OF 7704 MEDLINE
TI HTLV-related disease [editorial].

L2 ANSWER 71 OF 7704 MEDLINE {
TI Anti-ATLA (antibody to adult T-cell leukemia virus-associated antigen), highly positive in OKT4-positive

mature T-cell malignancies.

L2 ANSWER 72 OF 7704 MEDLINE
TI Atypical adult T-cell leukemia-lymphoma: diverse clinical manifestations of adult T-cell leukemia-lymphoma.

L2 ANSWER 73 OF 7704 MEDLINE
TI The human T-cell leukemia-lymphoma virus in the southeastern United States.

L2 ANSWER 74 OF 7704 MEDLINE
TI The histopathology of adult T-cell lymphoma/leukaemia in blacks from the Caribbean.

L2 ANSWER 75 OF 7704 MEDLINE
TI The human T-cell leukemia/lymphoma virus associated with American adult T-cell leukemia/lymphoma.

L2 ANSWER 76 OF 7704 MEDLINE
TI Human T-cell leukemia-lymphoma virus (HTLV) and human viral onc gene homologues.

L2 ANSWER 77 OF 7704 MEDLINE
TI Human T-cell leukaemia/lymphoma virus-associated lymphoreticular neoplasia in Jamaica.

L2 ANSWER 78 OF 7704 MEDLINE
TI Enhanced expression of human T-cell leukemia/lymphoma virus in neoplastic T cells induced to proliferate by phorbol ester and interleukin-2.

L2 ANSWER 79 OF 7704 MEDLINE
TI Presence of HTLV in a subset of T cells from an infected patient: some immunochemical properties of the infected cells.
L2 ANSWER 80 OF 7704 MEDLINE
TI Transmission of human T-cell leukemia virus (HTLV) into human cord blood T cells.

=> d 76 au,ti,so,py,ab

L2 ANSWER 76 OF 7704 MEDLINE
AU Gallo R C; Wong-Staal F
TI Human T-cell leukemia-lymphoma virus (HTLV) and human viral onc gene homologues.
SO Prog Clin Biol Res, (1983) 119 223-42.
Journal code: PZ5. ISSN: 0361-7742.
PY 1983

=> d ti 81-100

L2 ANSWER 81 OF 7704 MEDLINE

TI Human T-cell leukemia-lymphoma virus (HTLV): a progress report.

L2 ANSWER 82 OF 7704 MEDLINE
TI Epidemiology of HTLV-associated leukemia.

L2 ANSWER 83 OF 7704 MEDLINE
TI Association of the human type C retrovirus with a subset of adult T-cell cancers.

L2 ANSWER 84 OF 7704 MEDLINE
TI Establishment of an etiologic relationship between the human T-cell leukemia/lymphoma virus (HTLV) and adult T-cell leukemia.

L2 ANSWER 85 OF 7704 MEDLINE
TI Relatedness by nucleic acid hybridization of new isolates of human T-cell leukemia-lymphoma virus (HTLV) and demonstration of provirus in uncultured leukemic blood cells.

L2 ANSWER 86 OF 7704 MEDLINE
TI Human adult T-cell leukemia virus: complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA.

L2 ANSWER 87 OF 7704 MEDLINE
TI HTLV and AIDS [editorial].

L2 ANSWER 88 OF 7704 MEDLINE
TI Isolation of a T-lymphotropic retrovirus from a patient at risk for acquired immune deficiency syndrome (AIDS).

L2 ANSWER 89 OF 7704 MEDLINE
TI Isolation of human T-cell leukemia virus in acquired immune deficiency syndrome (AIDS).

L2 ANSWER 90 OF 7704 MEDLINE {
TI Proviral DNA of a retrovirus, human T-cell leukemia virus, in two patients with AIDS.

L2 ANSWER 91 OF 7704 MEDLINE
TI Common site of integration of HTLV in cells of three patients with mature T-cell leukaemia-lymphoma [retracted by Hahn B, Manzari V, Colombini S, Franchini G, Gallo RC, Wong-Staal F. In: Nature 1983 Sep 22-28;305(5932):340].

L2 ANSWER 92 OF 7704 MEDLINE
TI High incidence of human type-C retrovirus (HTLV) in family members of a HTLV-positive Japanese T-cell leukemia patient.

L2 ANSWER 93 OF 7704 MEDLINE
TI Identification of human T cell leukemia virus in a Japanese patient with adult T cell leukemia and cutaneous lymphomatous

vasculitis.
L2 ANSWER 94 OF 7704 MEDLINE
TI Human T-cell leukemia-lymphoma virus (HTLV): cloning of an integrated defective provirus and flanking cellular sequences.

L2 ANSWER 95 OF 7704 MEDLINE
TI A survey of human leukaemias for sequences of a human retrovirus.
L2 ANSWER 96 OF 7704 MEDLINE
TI Monoclonal antibody against human T cell leukemia virus p19 defines a human thymic epithelial antigen acquired during ontogeny.
L2 ANSWER 97 OF 7704 MEDLINE
TI Epidemiology of human T-cell leukemia/lymphoma virus.
L2 ANSWER 98 OF 7704 MEDLINE
TI Human T-cell leukemia/lymphoma virus: the retrovirus of adult T-cell leukemia/lymphoma.

L2 ANSWER 99 OF 7704 MEDLINE
TI Infection and transformation of fresh human umbilical cord blood cells by multiple sources of human T-cell leukemia-lymphoma virus ( HTLV).

L2 ANSWER 100 OF 7704 MEDLINE
TI Persistent in vitro infection by human T-cell leukemia-lymphoma virus (HTLV) of normal human T-lymphocytes from blood relatives of patients with HTLV-associated mature T-cell neoplasms.

=> d 86, 90, 94 au,ti,so,py,ab

L2 ANSWER 86 OF 7704 MEDLINE
AU Seiki M; Hattori S; Hirayama Y; Yoshida M
TI Human adult T-cell leukemia virus: complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA.
SO Proc Natl Acad Sci U S A, (1983 Jun) 80 (12) 3618-22. Journal code: PV3. ISSN: 0027-8424.
PY 1983
AB Human retrovirus adult T-cell leukemia virus (ATLV) has been shown to be closely associated with human adult T-cell leukemia (ATL) [Yoshida, M., Miyoshi, I. & Hinuma, Y. (1982) Proc. Natl. Acad. Sci. USA 79, 2031-2035]. The provirus of ATLV integrated in DNA of leukemia T cells from a patient with ATL was molecularly cloned and the complete nucleotide sequence of 9,032 bases of the proviral genome was determined. The provirus DNA contains two long terminal repeats (LTRs) consisting of 755 bases, one at each end, which are flanked by a 6-base direct repeat of the cellular DNA sequence. The nucleotides in the LTR could be arranged into a unique secondary structure, which could explain transcriptional termination within the 3' LTR but not in the 5' LTR. The nucleotide sequence of the provirus contains

three large open reading frames, which are capable of coding for proteins of 48,000, 99,000, and 54,000 daltons. The three open frames are in this order from the 5' end of the viral genome and the predicted 48,000-dalton polypeptide is a precursor of gag proteins, because it has an identical amino acid sequence to that of the NH2 terminus of human T-cell leukemia virus ( HTLV) p24. The open frames coding for 99,000- and 54,000-dalton polypeptides are thought to be the pol and env genes, respectively. On the 3' side of these three open frames, the ATLV sequence has four smaller open frames in various phases; these frames may code for 10,000-, 11,000-, 12,000-, and 27,000-dalton polypeptides. Although one or some of these open frames could be the transforming gene of this virus, in preliminary analysis, DNA of this region has no homology with the normal human genome.

L2 ANSWER 90 OF 7704 MEDLINE
AU Gelmann E P; Popovic M; Blayney D; Masur H; Sidhu G; Stahl R E; Gallo R C
TI Proviral DNA of a retrovirus, human T-cell leukemia virus, in two patients with AIDS.
SO Science, (1983 May 20) 220 (4599) 862-5.
Journal code: UJ7. ISSN: 0036-8075.
PY 1983
AB The acquired immune deficiency syndrome (AIDS) is characterized by T-lymphocyte dysfunction and is frequently accompanied by opportunistic infections and Kaposi's sarcoma. Human T-cell leukemia virus (HTLV) is associated with T-cell malignancies and { can transform T lymphocytes in vitro. In an attempt to find evidence of HTLV infection in patients with AIDS, DNA from samples of peripheral blood lymphocytes from 33 AIDS patients was analyzed by Southern blot-hybridization with a radiolabeled cloned HTLV DNA probe. Analysis of DNA from both the fresh (uncultured) lymphocytes and from T cells cultured with T-cell growth factor revealed the presence of integrated HTLV proviral sequences in lymphocytes from two of the patients, both of whom had antibody to HTLV. The proviral sequences could not be detected in blood samples obtained from these individuals at a later date, consistent with the possibility that the population of infected cells had become depleted.

L2 ANSWER 94 OF 7704 MEDLINE
AU Manzari V; Wong-Staal F; Franchini G; Colombini S; Gelmann E P; Oroszlan S; Staal S; Gallo R C
TI Human T-cell leukemia-lymphoma virus (HTLV): cloning of an integrated defective provirus and flanking cellular sequences.
SO Proc Natl Acad Sci U S A, (1983 Mar) 80 (6) 1574-8.
Journal code: PV3. ISSN: 0027-8424.
PY 1983
AB Human T-cell leukemia-lymphoma virus (HTLV) is the first unequivocal human retrovirus. Seroepidemiological and virus isolation studies indicate that HTLV is etiologically associated

with a subtype of adult T-cell malignancy. We have molecularly cloned approximately 1 kilobase of sequences derived from the 5' and 3' termini of the HTLV genome. Use of these clones as probes allowed isolation of a 9.8-kilobase EcoRI fragment from a genomic DNA library of an HTLV-infected neoplastic T-cell line (CR). Analysis of this clone revealed the presence of cellular sequences flanking approximately 5 kilobases of viral sequences including one long terminal repeat sequence. The 5' and 3' clones, as well as subclones derived from different regions of the genomic clone, were used as probes to compare integrated proviruses and viral RNA expression in different HLTV-infected neoplastic T cell lines. The results indicate that the infected cells are of clonal origin with respect to the virus integration sites and they express multiple viral mRNA species including a 35S RNA.

=> d ti 101-120

L2 ANSWER 101 OF 7704 MEDLINE
TI Isolation and transmission of human retrovirus (human t-cell leukemia virus).

L2 ANSWER 102 OF 7704 MEDLINE
TI Abundant transcription of a cellular gene in T cells infected with human T-cell leukemia-lymphoma virus.

L2 ANSWER 103 OF 7704 MEDLINE
TI HTLV: try Africa [letter].

L2 ANSWER 104 OF 7704 MEDLINE
TI Evidence for human T cell lymphoma-leukemia virus infection of family members of human T cell lymphoma-leukemia virus positive T cell leukemia-lymphoma patients.

L2 ANSWER 105 OF 7704 MEDLINE
TI Antibodies against three purified proteins of the human type C retrovirus, human T-cell leukemia-lymphoma virus, in adult T-cell leukemia-lymphoma patients and healthy Blacks from the Caribbean.

L2 ANSWER 106 OF 7704 MEDLINE
TI Herpesviruses, lymphocytes, and AIDS.

L2 ANSWER 107 OF 7704 MEDLINE
TI Guidelines for Confidentiality in Research on AIDS.

L2 ANSWER 108 OF 7704 MEDLINE
TI Establishment of retrovirus-, Epstein-Barr virus-positive B-lymphoblastoid cell lines derived from individuals at risk for acquired immune deficiency syndrome (AIDS).

L2 ANSWER 109 OF 7704 MEDLINE

TI Human T cell leukemia virus-1 antibodies not detected in AIDS.
L2 ANSWER 110 OF 7704 MEDLINE
TI IgG antibodies to HTLV-III associated antigens in patients with AIDS and at risk for AIDS in The Netherlands.

L2 ANSWER 111 OF 7704 MEDLINE
TI Detection of antibodies to human T-lymphotropic viruses type I and III in Japanese hemophiliacs.

L2 ANSWER 112 OF 7704 MEDLINE
TI HTLV: epidemiology and relationship to disease.
L2 ANSWER 113 OF 7704 MEDLINE
TI Adult T-cell leukemia/lymphoma in Jamaica and its relationship to human T-cell leukemia/lymphoma virus type I-associated lymphoproliferative disease.

L2 ANSWER 114 OF 7704 MEDLINE
TI Clinical implications of anti-HTLV antibody titer, abnormal lymphocytes in HTLV carriers and HTLV genome negative adult T-cell leukemia-lymphoma.

L2 ANSWER 115 OF 7704 MEDLINE
TI Clinical, immunological, ultrastructural, and cytogenetic studies in black patients with adult T-cell leukemia/lymphoma.

L2 ANSWER 116 OF 7704 MEDLINE
TI Clinical aspects of adult T-cell leukemia/lymphoma (ATL).

L2 ANSWER 117 OF 7704 MEDLINE
TI Nakahara memorial lecture. Human T-cell leukemia virus type I: molecular biology and its implications in adult T-cell leukemia.
L2 ANSWER 118 OF 7704 MEDLINE
TI Lymphadenopathy associated virus and its etiological role in AIDS.
L2 ANSWER 119 OF 7704 MEDLINE
TI HTLV and immunosuppression.

L2 ANSWER 120 OF 7704 MEDLINE
TI HTLV-III: the etiologic agent of AIDS.

=> d ti 121-140

L2 ANSWER 121 OF 7704 MEDLINE
TI Human retroviruses in health and disease.

L2 ANSWER 122 OF 7704 MEDLINE
TI Molecular characterization of human T-lymphotropic leukemia virus type III associated with the acquired immunodeficiency syndrome.

L2 ANSWER 123 OF 7704 MEDLINE
TI Protection of T cells against infectivity and cytopathic effect of HTLV-III in vitro.

L2 ANSWER 124 OF 7704 MEDLINE
TI Human retrovirus-induced IL-2 receptors and their possible role in transduction of continuous cell growth signal.

L2 ANSWER 125 OF 7704 MEDLINE
TI Interleukin-2 receptor expression in retrovirus associated adult T-cell leukemia.

L2 ANSWER 126 OF 7704 MEDLINE
TI Abnormal expression of interleukin-2 receptor (Tac antigen) in adult T-cell leukemia.

L2 ANSWER 127 OF 7704 MEDLINE
TI Characterization of simian retrovirus genome related to human T-cell leukemia virus type I.

L2 ANSWER 128 OF 7704 MEDLINE
TI BLV and HTLV-I: their unique genomic structures and evolutionary relationship.

L2 ANSWER 129 OF 7704 MEDLINE
TI Bovine leukemia virus, a distinguished member of the human T-lymphotropic virus family.

L2 ANSWER 130 OF 7704 MEDLINE
TI The pX region of HTLV-I.

L2 ANSWER 131 OF 7704 MEDLINE
TI Human T-cell leukemia virus specific antigens.

L2 ANSWER 132 OF 7704 MEDLINE
TI Structure and function of human leukemia and AIDS viruses.

L2 ANSWER 133 OF 7704 MEDLINE
TI The comparative molecular biology of HTLV-I and HTLV-II.

L2 ANSWER 134 OF 7704 MEDLINE
TI Nucleotide sequence analysis of human T-cell leukemia virus type II.

L2 ANSWER 135 OF 7704 MEDLINE
TI Pseudotype viruses bearing envelope antigens of Japanese isolates of human T-cell leukemia viruses type I.

L2 ANSWER 136 OF 7704 MEDLINE
TI Structural and antigenic characterization of the proteins of human T-cell leukemia viruses and their relationships to the

gene products of other retroviruses.

L2 ANSWER 137 OF 7704 MEDLINE
TI Kaplan memorial lecture. The family of human lymphotropic retroviruses called HTLV: HTLV-I in adult T-cell leukemia (ATL), HTLV-II in hairy cell leukemias, and HTLV-III in AIDS.

L2 ANSWER 138 OF 7704 MEDLINE
TI Transmission of ATLV (HTLV-I) through blood transfusion.
L2 ANSWER 139 OF 7704 MEDLINE
TI Infectious transmission of human T-cell leukemia virus to animals.
L2 ANSWER 140 OF 7704 MEDLINE
TI Structural and epidemiological features of primate lymphotropic retroviruses.

=> d 122, 128, 130, 131, 132, 133, 134, 136, au,ti,so,py,ab
L2 ANSWER 122 OF 7704 MEDLINE
AU Wong-Staal F; Hahn B H; Shaw G M; Arya S K; Harper M; Gonda M; Gilden R; Ratner L; Starcich B; Okamoto T; et al
TI Molecular characterization of human T-lymphotropic leukemia virus type III associated with the acquired immunodeficiency syndrome. SO Princess Takamatsu Symp, (1984) 15 291-300.
Journal code: HHI.
PY 1984
AB A T-lymphotropic retrovirus with cytopathic but not immortalizing activity has been isolated repeatedly from patients with acquired immune deficiency (AIDS) or lymphadenopathy syndrome (LAS) and successfully transmitted to a T-cell line (HT) for continuous production. Seroepidemiology data and the OKT4 tropism and cytopathogenicity of this virus indicate it is the etiological agent of AIDS. We have cloned HTLV-III genomes using three approaches: (1) cDNA clones were obtained from a cDNA plasmid library constructed from RNA of purified virions using oligo (dT) primers; (2) unintegrated provirus clones were obtained from Hirt supernatants of acutely infected H9 cells using virus from H9/ HTLV-III; (3) clones of integrated provirus with flanking cellular sequences were obtained from a genomic DNA library of H9/ HTLV-III. Analyses of these clones show that the HTLV-III genome is similar in size to those of HTLV -I and HTLV-II and contains a gene that functions as a transcriptional activator. Different isolates of HTLV-III display greater polymorphism than different isolates of HTLV -I among each other, possibly due to the highly replicative nature of HTLV-III. Viral sequences could be detected in fresh lymph node tissues of some AIDS patients, but even in the positive samples the number of infected cells is small (less than 1%). In both fresh tissues that are positive for viral sequences and HTLV-III infected cell lines, a substantial amount of unintegrated viral DNA is present in addition to integrated provirus. This is an unusual finding for retroviruses

but may be significant in the cytopathicity of HTLV-III as has been proposed for some avain retroviruses.

L2 ANSWER 128 OF 7704 MEDLINE
AU Sagata N; Ikawa Y
TI BLV and HTLV-I: their unique genomic structures and evolutionary relationship.
SO Princess Takamatsu Symp, (1984) 15 229-40. Ref: 30
Journal code: HHI.
PY 1984
AB We have compared the sequences of the entire genomes of bovine leukemia virus (BLV) and human T-cell leukemia virus type I ( HTLV-I). Both the gag and pol genes show overall strong homologies between the two retroviruses, indicating their close evolutionary relationship. However, a surface glycoprotein portion of the env gene shows little if any homology, probably reflecting a difference in their host range. These retroviruses appear to harbour a gag precursor-cleaving protease, a not yet experimentally identified viral protein, between their gag and pol genes. Most interestingly, the 3' end portion of the BLV genome (designated pXBL) contains a long open reading frame that has a typical protein-coding property. The product of this open reading frame has now been identified as a protein of 38,000 daltons, which is produced by a spliced mRNA. We note that its amino acid sequence shows appreciable homology, especially in its N-terminal quarter, to that of the HTLV-I counterpart (pX), and we thus suggest that BLV pXBL and HTLV-I pX has diverged from a common ancestral gene. Finally and very importantly, comparisons of the best conserved pol sequences and overall genomic organizations between BLV and several other oncoviruses allow us to propose that BLV and HTLV-I constitute a novel group of Oncovirinae, designated here as type "E."

L2 ANSWER 130 OF 7704 MEDLINE
AU Hatanaka M; Kobayashi N
TI The pX region of HTLV-I.
SO Princess Takamatsu Symp, (1984) 15 205-17.
Journal code: HHI.
PY 1984
AB Gallo and his coworkers isolated a retrovirus (HTLV) from human cells derived from T-cell leukemia and lymphoma. Hinuma and his coworkers isolated independently a similar virus from a cell line derived from adult T-cell leukemia (ATL) patient. The occurrence of ATL correlates with the formation of antibody to ATL associated antigens or ATLA. To understand the etiological relationship between ATL and HTLV, we analyzed the antigens termed ATLA and found that they are polypeptides encoded by HTLV genome. We further studied the genome of HTLV and its gene expression in cells as well as in a cell-free translation system. We focused on a defective type HTLV produced from a cell line MT-2 that transforms normal lymphocytes most efficiently.

The 24S defective gene of HTLV consists of a fused gene of gag-pXs and is amplified at the proviral state. The in vitro translation experiments revealed that the 24S defective gene of HTLV directs the synthesis of p28 of ATLA. By the sequence analysis of the amplified gag-pXs fused genes, we found that a carboxy terminal portion of p28 is translat { {ed from a pX-0 region. We further investigated a function of the gag-pX-0 fusion protein, p28. The p28 has an associated protein kinase activity that requires manganese instead of magnesium and phosphorylates the serine residue specifically. Another defective HTLV with a genomic 32S RNA was analyzed. The 32S defective genomic RNA forms a subgenomic 20S RNA in cells. The 20S mRNA is a transcript of an env-pXs fused genome and directs the synthesis of a fused glycoprotein, gp68 of ATLA. The sequence analysis of a cl {oned cDNA derived from the subgenomic 20S mRNA revealed that a coding frame of the entire pX-IV region is translated. In fact, an antibody against synthetic polypeptides of the pX-IV, immunoprecipitated the gp68. These results demonstrate at the first time that the pX-0 and pX-IV of HTLV genome are expressed in human cells. The biological activities of the fused pXs proteins are also discussed. Human T-cell leukemia virus type I (HTLV-I), a family of human retrovirus and the predicted causative age {nt of human adult T-cell leukemia/lymphoma (ATL) consists of the gag, pol, env, and pX regions (1).(ABSTRACT TRUNCATED AT 400 WORDS)

L2 ANSWER 131 OF 7704 MEDLINE
AU Lee T H; Coligan J E; Essex M
TI Human T-cell leukemia virus specific antigens.
SO Princess Takamatsu Symp, (1984) 15 197-203. Ref: 27
Journal code: HHI.
PY 1984
AB Type I and type II human T-cell leukemia viruses (HTLV) contain in their genomes three structural genes, gag, pol, and env and a putative transforming gene, lor. Using a living cell membrane immunofluorescence assay, antibodies to surface-expressed env gene products of HTLV-MA have been detected in healthy carriers living in the HTLV-I endemic areas, and in patients with adult T-cell leukemia/lymphoma (ATLL). Similar antibody reactivities were detected in patient MO, from whom HTLV-II was first isolated, and in a proportion of patients with acquired immune deficiency syndrome (AIDS). Amino acid sequence homology between env gene products of HTLV-I and HTLV-II provides the molecular basis for the observed serological crossreactivity. Detection of HTLV-specific antibody in a proportion of AIDS patients suggested that agents related to HTLV-I may be the etiological cause of AIDS. Several lines of evidence have now suggested that HTLV-III is the etiological agent of AIDS. Flanked by the env gene and 3' long terminal repeat (LTR) is a region originally described by Seiki et al. as "X." A 42 kdalton and a 38 kdalton product have been detected in

HTLV-I and HTLV-II transformed cells, respectively. These two proteins appear to be translated from a long open reading (lor) frame in the X region, and from a yet to be defined region upstream to the lor gene. The identification of lor products provides direct evidence for the presence of previously unidentified functional genes in { HTLV-I and HTLV-II.(ABSTRACT TRUNCATED AT 250 WORDS)

L2 ANSWER 132 OF 7704 MEDLINE
AU Haseltine W A; Sodroski J; Rosen C
TI Structure and function of human leukemia and AIDS viruses.
SO Princess Takamatsu Symp, (1984) 15 187-96. Ref: 24
Journal code: HHI.
PY 1984
AB Gene expression directed by the long terminal repeats of human T-lymphotropic viruses is activated in trans by factors present in virus-infected cells. Trans-activation probably plays a major role in stimulating virus production and may also mediate some of the effects of viral infection on the host cell.

L2 ANSWER 133 OF 7704 MEDLINE
AU Rosenblatt J; Wachsman W; Shimotohno K; Slamon D; Chen I S
TI The comparative molecular biology of HTLV-I and HTLV-II.

SO Princess Takamatsu Symp, (1984) 15 177-85. Ref: 28
Journal code: HHI.
PY 1984
AB The human T-cell leukemia viruses (HTLV) I and II, have been implicated in naturally occurring T-cell malignancies in man. We are engaged in ongoing comparative studies of HTLV-I and HTLV-II in our laboratory. We have isolated a replication-competent clone of HTLV-II, as well as several defective HTLV-II proviruses from the Mo-T hairy-cell leukemia line. HTLV-II is able to transform normal T-lymphocytes, and can replicate in both T- and B-cell lines. We have devised a convenient system allowing direct transfection of the HTLV-II genome into a B-cell line, followed by selection of HTLV-infected cells. Transfection studies with HTLV -II indicate that the virus can replicate in lymphoid cells, but not in fibroblasts. Transfection of recombinant constructs demonstrates that the viral long terminal repeat (LTR) can function as a promoter in lymphoid cells, but not in fibroblasts, suggesting a role for the viral LTR in conferring target cell specificity. Structural similarities between the HTLV-I and HTLV-II LTRs, including the presence of similar repeated base sequences in the U3 region, may account for this LTR specificity. The X region of HTLV-II has been sequenced and compared to that of HTLV-I. We have identified an mRNA species encoded by the major open reading frames in the X region of HTLV-I and HTLV-II and have located the splice acceptor site. Using antisera generated to short peptide sequences encoded by X, we have identified

specific X-encoded viral proteins in HTLV infected cells.(ABSTRACT TRUNCATED AT 250 WORDS)

L2 ANSWER 134 OF 7704 MEDLINE
AU Shimotohno K; Takahashi Y; Shimizu N; Takano M; Miwa M; Sugimura T TI Nucleotide sequence analysis of human T-cell leukemia virus type II. SO Princess Takamatsu Symp, (1984) 15 165-75. Ref: 23
Journal code: HHI.
PY 1984
AB The total nucleotide sequence of an infectious clone of human T-cell leukemia virus type II (HTLV-II) provirus was determined. The provirus has 8,952 nucleotides with a long terminal repeat (LTR) at each end. The LTR consists of 341 +/- 1 bases of U3, 248 +/- 1 bases of R, and 201 bases of U5 regions. There are gag, pol, and env coding frames in this order from the 5' end of the provirus as in other avian or mammalian retroviruses. A coding frame that can code 178 amino acid residues found between gag and pol is supposed to be for a protease that hydrolyses a gag precursor protein to matured gag proteins. The gag and protease genes and the pol and env genes, respectively, partly overlap. In the region termed X between env and 3' LTR, there are three major open reading frames. Oligopeptides deduced from the sequence of one of the open reading frame in HTLV-I were synthesized chemically, and antibodies against these peptides were raised in rabbits. With these antibodies, 41 kdalton and 38 kdalton proteins were detected in cells infected with HTLV-I and HTLV-II, respectively.

L2 ANSWER 136 OF 7704 MEDLINE
AU Oroszlan S; Copeland T D; Rice N R; Smythers G W; Tsai W P; Yoshinaka Y; Shimotohno K
TI Structural and antigenic characterization of the proteins of human T-cell leukemia viruses and their relationships to the gene products of other retroviruses.
SO Princess Takamatsu Symp, (1984) 15 147-57. Ref: 32
Journal code: HHI.
PY 1984
AB The primary structure analysis of the gag gene products of human T-cell leukemia virus (HTLV)-ICR has been nearly completed. A comparison of the amino acid sequences with the published nucleotide sequence of HTLV-IATK established that i) p19 which is known to share antigenic determinants with a protein present in normal thymic epithelium, is nevertheless virally coded. ii) The gene order and complete primary structure of the gag precursor (Pr55) which has been shown to be myristylated (My) at its N-terminus is My-p19-p24-p15-OH; and iii) the Pr55gag amino acid sequences of HTLV-ICR and HTLV-IATK are nearly identical showing only a single residue difference in the C-terminal region of p15. Antibodies to synthetic peptides

inferred from the nucleotide sequence of the env gene of HTLV-IATK were also raised and used to identify and purify env precursor gPr62-68, surface glycoprotein gp46-51 and transmembrane protein p21. While most of the peptide sera were shown to be subgroup specific some of them detected antigenic determinants shared between protein homologs of viruses of subgroups I and II. Partial or complete amino acid sequences of both the gag and env gene coded proteins of bovine leukemia virus (BLV) structural proteins have also been determined. These extensive protein data together with nucleotide sequences confirm and extend our initial finding that HTLV and BLV are structurally and antigenically related and may have originated from common ancestor. The structural and immunological studies revealed also relationships between HTLV and a number of type C and type D retroviruses studied. One of the highly conserved sequences is shared by the transmembrane proteins of these retroviruses which have been implicated in immunosuppression. It is conceivable that these common regions have common biological function. Two previously unidentified proteins of BLV have also been purified and structurally characterized. Nucleotide sequences capable of coding for related products are present in HTLV . The nature and possible biological functions of these new BLV proteins and the putative HTLV gene products will be discussed. The size and complexity of the genome of the replication competent retroviruses are similar but not identical. The 35S RNA of all replication competent helper viruses is divided into three genes encoding the viral structural proteins: the gag (group-specific antigen) gene codes for the internal structural proteins, the pol (polymerase) gene codes for the enzymes protease, reverse transcriptase and endonuclease and the env (envelope) gene codes for the proteins of the viral envelope.(ABSTRACT TRUNCATED AT 400 WORDS)
=> d ti 141-160

L2 ANSWER 141 OF 7704 MEDLINE
TI Retroviruses in human lymphoma/leukemia.

L2 ANSWER 142 OF 7704 MEDLINE
TI A study of anti-ATLA (antibodies to adult T-cell leukemia virus- associated antigens) in healthy subjects--a sero-epidemiological study on residents of Kagoshima prefecture and a family study of patients with adult T-cell leukemia-lymphoma and other diseases.

L2 ANSWER 143 OF 7704 MEDLINE
TI Defective human T-cell leukemia virus in adult T-cell leukemia patients.

L2 ANSWER 144 OF 7704 MEDLINE
TI Electron microscopic comparison of adult T-cell leukemia associated virus (ATLV) and murine leukemia virus (MuLV).

L2 ANSWER 145 OF 7704 MEDLINE
TI [Is it possible to contain the danger of AIDS to health care personnel ?].
E possible contenere il pericolo di AIDS per il personale sanitario?.

L2 ANSWER 146 OF 7704 MEDLINE
TI [Is there a risk of AIDS for health care personnel?].
Esiste un rischio di AIDS per il personale sanitario?.

L2 ANSWER 147 OF 7704 MEDLINE
TI A comparative ultrastructural study of virions in human pre-AIDS and simian AIDS.

L2 ANSWER 148 OF 7704 MEDLINE
TI The epidemic of acquired immunodeficiency syndrome (AIDS) and suggestions for its control in drug abusers.

L2 ANSWER 149 OF 7704 MEDLINE
TI Possible viral etiology of childhood acute lymphosarcoma-cell leukaemia in Kenya.

L2 ANSWER 150 OF 7704 MEDLINE
TI Virus-associated lymphomas, leukaemias and immunodeficiencies in Africa.

L2 ANSWER 151 OF 7704 MEDLINE
TI Human T-cell leukaemia virus in Africa: possible roles in health and disease.

L2 ANSWER 152 OF 7704 MEDLINE
TI Etiology of endemic Kaposi's sarcoma.

L2 ANSWER 153 OF 7704 MEDLINE
TI Natural antibodies to simian type-C viruses and human retrovirus HTLV in patients with lymphoid malignancies.

L2 ANSWER 154 OF 7704 MEDLINE
TI Human T-cell leukemia virus: transformation in vitro of nonhuman primate T-lymphocytes and experimental inoculation of nonhuman primates.

L2 ANSWER 155 OF 7704 MEDLINE
TI Virologic, immunologic, and epidemiologic associations with AIDS among gay males in a low incidence area.

L2 ANSWER 156 OF 7704 MEDLINE
TI Soluble factors inhibitory for T-cell-dependent immune responses in patients with the acquired immune deficiency syndrome and its prodromes.

L2 ANSWER 157 OF 7704 MEDLINE
TI Pediatric acquired immunodeficiency syndrome.

L2 ANSWER 158 OF 7704 MEDLINE
TI Seroepidemiology of human T-cell leukemia virus in the French West Indies: antibodies in blood donors and patients with lymphoproliferative diseases who do not have AIDS.

L2 ANSWER 159 OF 7704 MEDLINE
TI Correlation between exposure to human T-cell leukemia-lymphoma virus-III and the development of AIDS.

L2 ANSWER 160 OF 7704 MEDLINE
TI Constitutive production and characterization of interferon-gamma in a human T-lymphoblastoid cell line transformed by a human retrovirus.

=> d ti 161-180

L2 ANSWER 161 OF 7704 MEDLINE
TI Recent progress in adult T-cell leukemia research: transmission of human T-cell leukemia virus to animals.

L2 ANSWER 162 OF 7704 MEDLINE
TI Molecular approach to adult T-cell leukemia.

L2 ANSWER 163 OF 7704 MEDLINE
TI When will prevention of HTLV-III infection be possible?.
L2 ANSWER 164 OF 7704 MEDLINE
TI Gallium scintigraphy in adult T-cell leukemia-lymphoma and angioimmunoblastic lymphoadenopathy with dysproteinemia.
L2 ANSWER 165 OF 7704 MEDLINE
TI In vitro transformation of human cord blood and bone marrow T lymphocytes by HTLV.

L2 ANSWER 166 OF 7704 MEDLINE
TI Acquired immunodeficiency syndrome (AIDS) in Africans.
L2 ANSWER 167 OF 7704 MEDLINE
TI [AIDS in tropical areas: Haitian and African foci].
Le SIDA en region tropicale: les foyers Haitien et Africain.
L2 ANSWER 168 OF 7704 MEDLINE
TI [Pseudo-mycosis fungoides T-lymphoma associated with an HTLV retrovirus in an African].
Lymphome T pseudo-mycosis fongoide chez un africain associe `a un retrovirus HTLV.

L2 ANSWER 169 OF 7704 MEDLINE
TI The acquired immune deficiency syndrome.

L2 ANSWER 170 OF 7704 MEDLINE
TI Human T-cell leukemia virus: its discovery and role in leukemogenesis and immunosuppression.

L2 ANSWER 171 OF 7704 MEDLINE
TI [New knowledge on the molecular mechanism of activation of oncogenes and effect of oncogene DNA on protein synthesis].
Neue Erkenntnisse uber den molekularen Mechanismus der Aktivierung von Onkogenen und uber den Einfluss von onkogener DNA auf die Proteinsynthese.

L2 ANSWER 172 OF 7704 MEDLINE
TI [Acquired immunodeficiency syndrome (AIDS): new reports]. Zespol nabytej niewydolnosci immunologicznej AIDS--dalsze doniesienia.

L2 ANSWER 173 OF 7704 MEDLINE
TI Acquired immune deficiency syndrome.

L2 ANSWER 174 OF 7704 MEDLINE
TI [AIDS--a virus infection?].
AIDS--eine Virusinfektion?.

L2 ANSWER 175 OF 7704 MEDLINE
TI Transfusion-mediated spread of the human T-cell leukemia virus in chronic hemodialysis patients in a heavily endemic area, Nagasaki.

L2 ANSWER 176 OF 7704 MEDLINE
TI Search for possible routes of vertical and horizontal transmission of adult T-cell leukemia virus.

L2 ANSWER 177 OF 7704 MEDLINE
TI Comparison of the entire genomes of bovine leukemia virus and human T-cell leukemia virus and characterization of their unidentified open reading frames.

L2 ANSWER 178 OF 7704 MEDLINE
TI Detection of HLA-D-region-associated antigens on the surface of adult T-cell leukemia virus particles by immunoelectron microscopy.

L2 ANSWER 179 OF 7704 MEDLINE
TI Ultrastructural study of type C virus particles in phytohemagglutinin-stimulated lymphocytes from healthy adults seropositive to adult T-cell leukemia-associated antigens.

L2 ANSWER 180 OF 7704 MEDLINE
TI Adult T-cell leukemia-lymphoma in the Hokuriku District and presentation of a case in hematological remission after cryptococcus infection.

{
=> d 177, au,ti,so,py,ab

L2 ANSWER 177 OF 7704 MEDLINE
AU Sagata N; Yasunaga T; Ohishi K; Tsuzuku-Kawamura J; Onuma

M; Ikawa Y TI Comparison of the entire genomes of bovine leukemia virus and human T-cell leukemia virus and characterization of their unidentified open reading frames.
SO EMBO J, (1984 Dec 20) 3 (13) 3231-7.
Journal code: EMB. ISSN: 0261-4189.
PY 1984
AB We have compared the sequence of the entire genomes of bovine leukemia virus (BLV) and human T-cell leukemia virus type I ( HTLV-I). Both the gag and pol genes show overall strong homologies indicating the close evolutionary relationship of the two retroviruses. However, a surface glycoprotein portion of the env gene shows no appreciable homology, which probably reflects a difference in their host ranges. The 3' end portion of the BLV genome (designated as pXBL) contains an unidentified long open reading frame that has a typical protein-coding property. The potential product of this open reading frame may be a glycoprotein of approximately 40 000 daltons. We note that its amino acid sequence shows low but appreciable homology, especially in its N-terminal quarter, to that of the HTLV-I counterpart (pX product), and we thus suggest that BLV pXBL and HTLV-I pX have diverged from a common ancestral gene. It is tentatively concluded that both the putative pXBL and pX products are respectively produced from a spliced mRNA.

=> d 181-200 ti

L2 ANSWER 181 OF 7704 MEDLINE
TI Electron microscopic study of cell lines established from adult T-cell leukemia--coexistence of adult T-cell leukemia virus and Epstein-Barr virus.

L2 ANSWER 182 OF 7704 MEDLINE
TI Outbreak of persistent, unexplained, generalized lymphadenopathy with immunological abnormalities in drug addicts in Milan.
L2 ANSWER 183 OF 7704 MEDLINE
TI [AIDS: does the control gene pX poison the lymphocytes?]. AIDS: Vergiftet das Schalt-Gen pX die Lymphozyten?.

L2 ANSWER 184 OF 7704 MEDLINE
TI Phenotypic characterization and ontogeny of components of the human thymic microenvironment.

L2 ANSWER 185 OF 7704 MEDLINE
TI Immunologic abnormalities in the acquired immunodeficiency syndrome (AIDS).

L2 ANSWER 186 OF 7704 MEDLINE
TI Successful chemotherapy with deoxycoformycin in adult T-cell lymphoma-leukaemia.

L2 ANSWER 187 OF 7704 MEDLINE
TI Acquired immunodeficiency syndrome (AIDS).

L2 ANSWER 188 OF 7704 MEDLINE
TI [Is human T-cell leukemia virus the cause of acquired immunodeficiency syndrome?].
Czy retrowirus ludzkich bialaczek T komorkowych jest przyczyna nabytego zespolu niedoborow immunologicznych?.

L2 ANSWER 189 OF 7704 MEDLINE
TI [Acquired immunodeficiency syndrome].
Zespol nabytej niewydolnosci immunologicznej--AIDS.

L2 ANSWER 190 OF 7704 MEDLINE
TI Long terminal repeat structure of an American isolate of type I human T-cell leukemia virus.

L2 ANSWER 191 OF 7704 MEDLINE
TI Morphology of the retroviruses associated with AIDS and SAIDS.

L2 ANSWER 192 OF 7704 MEDLINE
TI T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. {

L2 ANSWER 193 OF 7704 MEDLINE
TI The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus.

L2 ANSWER 194 OF 7704 MEDLINE
TI Molecular cloning of AIDS-associated retrovirus.

L2 ANSWER 195 OF 7704 MEDLINE
TI Molecular cloning of lymphadenopathy-associated virus.

L2 ANSWER 196 OF 7704 MEDLINE {
TI A new monoclonal antibody recognizing an antigen of human lymphocytes similar or identical to Tac antigen.

L2 ANSWER 197 OF 7704 MEDLINE
TI Clonal selection of human T-cell leukemia virus-infected cells in vivo and in vitro.

L2 ANSWER 198 OF 7704 MEDLINE
TI T4 positive human neoplastic cell lines susceptible to and permissive for HTLV-III [letter].

L2 ANSWER 199 OF 7704 MEDLINE
TI HTLV-III seropositivity in European haemophiliacs exposed to Factor VIII concentrate imported from the USA.

L2 ANSWER 200 OF 7704 MEDLINE
TI Blood transfusion, haemophilia, and AIDS [editorial].

=> d 194, 195, au,ti,so,py,ab

L2 ANSWER 194 OF 7704 MEDLINE
AU Luciw P A; Potter S J; Steimer K; Dina D; Levy J A
TI Molecular cloning of AIDS-associated retrovirus.
SO Nature, (1984 Dec 20-1985 Jan 2) 312 (5996) 760-3.
Journal code: NSC. ISSN: 0028-0836.
PY 1984
AB Retroviruses cause a wide variety of diseases in avian and mammalian species. Human acquired immune deficiency syndrome (AIDS) leads to collapse of the immune system and death by a wide variety of opportunistic infections; unusual forms of cancer are associated with this syndrome. Retroviruses have been recovered from tissues of AIDS patients and from patients with related conditions. These similar newly-isolated viruses are lymphadenopathy-associated virus (LAV), human T-cell lymphotropic virus (HTLV-III) and AIDS-associated retrovirus (ARV-2). We have identified a RNA genome of approximately 9 kilobases (kb) in virions purified from the culture medium of a human T-cell tumour line infected with ARV-2. A cDNA probe made from viral RNA detected circular DNA molecules and proviral forms in infected cells. We prepared a library of infected cell DNA. Recombinant phage included those with a 9.5-kb proviral DNA and viral DNA permuted with respect to the single EcoRI site. Comparison of three ARV isolates from different AIDS patients revealed polymorphism of restriction endonuclease sites.

L2 ANSWER 195 OF 7704 MEDLINE
AU Alizon M; Sonigo P; Barre-Sinoussi F; Chermann J C; Tiollais P; Montagnier L; Wain-Hobson S
TI Molecular cloning of lymphadenopathy-associated virus. SO Nature, (1984 Dec 20-1985 Jan 2) 312 (5996) 757-60. Journal code: NSC. ISSN: 0028-0836.
PY 1984
AB Lymphadenopathy-associated virus (LAV) is a human retrovirus first isolated from a homosexual patient with lymphadenopathy syndrome, frequently a prodrome or a benign form of acquired immune deficiency syndrome (AIDS). Other LAV isolates have subsequently been recovered from patients with AIDS or pre-AIDS and all available data are consistent with the virus being the causative agent of AIDS. The virus is propagated on activated T lymphocytes and has a tropism for the T-cell subset OKT4 (ref. 6), in which it induces a cytopathic effect. The major core protein of LAV is antigenically unrelated to other known retroviral antigens. LAV-like virus {es have more recently been independently isolated from patients with AIDS and pre-AIDS. These viruses, called human T-cell leukaemia/lymphoma virus type III (HTLV-III) and AIDS-associated retrovirus (ARV), seem to have many characteristics in common with LAV and probably represent independent isolates of the LAV prototype. We have sought to characterize LAV by the molecular cloning of its genome. A cloned LAV complementary DNA was used to screen a

library of recombinant phages constructed from the genomic DNA of LAV-infected T lymphocytes. Two families of clones were characterized which differ in a restriction site. The viral genome is longer than any other human retroviral genome (9.1-9.2 kilobases).

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=> s htlv
L3  2149 HTLV

=> s clone?
L4 95134 CLONE?

=> s l3 and l4
L5   334 L3 AND L4

=> sort
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SORT ENTIRE ANSWER SET? (Y)/N:y
ENTER SORT FIELDS AND SORT DIRECTION (?):py
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L6    334 SORT L5 PY

=> d ti 1-10

L6   ANSWER 1 OF 334  CA  COPYRIGHT 1995 ACS
TI   Human T cell hybridomas secreting immune interferon

L6   ANSWER 2 OF 334  CA  COPYRIGHT 1995 ACS
TI   Expression of cellular homologs of retroviral onc genes in
human hematopoietic cells

L6   ANSWER 3 OF 334  CA  COPYRIGHT 1995 ACS
TI   Molecular characterization of genome of a novel human
T-cell leukemia virus

L6   ANSWER 4 OF 334  CA  COPYRIGHT 1995 ACS
TI   Homology of human T-cell leukemia virus envelope gene with
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class I HLA gene

L6 ANSWER 5 OF 334 CA COPYRIGHT 1995 ACS
TI Human adult T-cell leukemia virus: complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA

L6 ANSWER 6 OF 334 CA COPYRIGHT 1995 ACS
TI Human T-cell leukemia-lymphoma virus (HTLV): cloning of an integrated defective provirus and flanking cellular sequences

L6 ANSWER 7 OF 334 CA COPYRIGHT 1995 ACS
TI Abundant transcription of a cellular gene in T cells infected with human T-cell leukemia-lymphoma virus

L6 ANSWER 8 OF 334 CA COPYRIGHT 1995 ACS
TI Rat T-cell clone formation by human T cell leukemia virus (HTLV)

L6 ANSWER 9 OF 334 CA COPYRIGHT 1995 ACS
TI Retrovirus-induced expression of interleukin 2 receptors on cells of human B-cell lineage

L6 ANSWER 10 OF 334 CA COPYRIGHT 1995 ACS
TI Molecular characterization of human T-cell leukemia (lymphotropic) virus type III in the acquired immune deficiency syndrome
=> d 10 au,ti,so,py,ab

L6 ANSWER 10 OF 334 CA COPYRIGHT 1995 ACS
AU Shaw, George M.; Hahn, Beatrice H.; Arya, Suresh K.; Groopman, Jerome E.; Gallo, Robert C.; Wong-Staal, Flossie
TI Molecular characterization of human T-cell leukemia (lymphotropic) virus type III in the acquired immune deficiency syndrome SO Science (Washington, D. C., 1883-) (1984), 226(4679), 1165-71 CODEN: SCIEAS; ISSN: 0036-8075
PY 1984
AB The human T-cell leukemia (lymphotropic) virus type III ( HTLV-III) appears to be central to the causation of the acquired immune deficiency syndrome (AIDS). Two full-length integrated proviral DNA forms of HTLV-III were cloned and analyzed, and DNA sequences of the virus in cell lines and fresh tissues from patients with AIDS or AIDS-related complex (ARC) characterized. Coclusions are, HTLV-III is an exogenous human retrovirus, approx. 10 kilobases in length, that lacks nucleic acid sequences derived from normal human DNA; HTLV-III, unlike HTLV types I and II, shows substantial diversity in its genomic restriction enzyme cleavage pattern; HTLV-III persists in substantial amts. in cells as unintegrated linear DNA, an uncommon property that has been linked to the cytopathic effects of certain animal retroviruses; and HTLV-III viral DNA can be detected in low levels in fresh (primary) lymphoid tissue of a

minority of patients with AIDS or ARC but appears not to be present in Kaposi's sarcoma tissue. These findings have important implications concerning the biol. properties of HTLV-III and the pathophysiol. of AIDS and Kaposi's sarcoma.

=> d his

(FILE 'HOME' ENTERED AT 14:21:32 ON 18 MAR 95)
SET PAGELENGTH SCROLL

FILE 'MEDLINE' ENTERED AT 14:22:03 ON 18 MAR 95
L1 7704 S HTLV
L2 7704 SORT L1 PY

FILE 'CA' ENTERED AT 14:44:27 ON 18 MAR 95
L3 2149 S HTLV
L4 95134 S CLONE?
L5 334 S L3 AND L4
L6 334 SORT L5 PY

=> s (gp120 or gp160 or gp41 or env? or p25 or p16 or p18 or gag)(p)express?

| | | |
|---|---|---|
| | 197 | GP120 |
| | 80 | GP160 |
| | 112 | GP41 |
| | 336871 | ENV? |
| | 694 | P25 |
| | 1027 | P16 |
| | 656 | P18 |
| | 995 | GAG |
| | 210233 | EXPRESS? |
| L1 | 5557 | (GP120 OR GP160 OR GP41 OR ENV? OR P25 OR P16 OR P18 OR GAG )(P )EXPRESS? |

=> s aids or hiv or htlv-III or lav

| | | |
|---|---|---|
| | 60412 | AIDS |
| | 1931 | HIV |
| | 937 | HTLV |
| | 285606 | III |
| | 578 | HTLV-III (HTLV(W)III) |
| | 472 | LAV |
| L2 | 61258 | AIDS OR HIV OR HTLV-III OR LAV |

=> s l1 and l2

| | | |
|---|---|---|
| L3 | 594 | L1 AND L2 |

=> d kwic 1

US PAT NO: 5,397,696 [IMAGE AVAILABLE] L3: 1 of 594
SUMMARY:

BSUM(6)

High . . . 1988; 26:339-351; Brindle et al., Epidemiol. Infect. 1988; 100:153-156; Brabin et al., Int. J. Cancer 1989; 44:59-62; Re et al., **AIDS** Res. Hum. Retroviruses 1989; 5:551-554; Armstrong et al., Am. J. Phys. Anthropol. 1990; 81:465-470; Garruto et al., Am. J. Hum.. . .
DETDESC:

DETD(42)

One culture, designated PNG-1, derived from a 20-year old Hagahai man, who had IgG antibodies against HTLV-I **gag** and **env**-encoded proteins by Western immunoblot, exhibited virus-specific fluorescence in approximately 1% of cells at two weeks, but cell growth remained sluggish. . . the establishment of a T-cell line which grew rapidly, but remained dependent on exogenous interleukin 2. The percentage of cells

**expressing** viral antigen, as determined by indirect immunofluorescence, increased to more than 85% at 39 days following co-cultivation with MOLT-3 cells. . .

DETDESC:

DETD(55)

A . . . found, indicating the presence of quasispecies. The phenomenon of multiple variants within a single individual has been described for both **HIV** (Saag et al., Nature 1988; 354:440-444; and Goodenow et al., J. **AIDS** 1989; 2:344-352) and HTLV-I (Daenke et al., J. Virol. 1990; 64:1278-1282).

=> d 2-10

2. 5,395,753, Mar. 7, 1995, Method for diagnosing rheumatoid arthritis; Ramesh K. Prakash, 435/7.1, 5, 6, 7.9, 7.92, 21; 436/506, 513, 543 [IMAGE AVAILABLE]

3. 5,393,449, Feb. 28, 1995, Personal cleansing stamped synbar containing alkyl glyceryl ether sulfonate and acyl isethionate; Neil W. Jordan, et al., 252/121, 134, 174, 554, 557, DIG.16 [IMAGE AVAILABLE]

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5. 5,387,744, Feb. 7, 1995, Avirulent microbes and uses therefor: Salmonella typhi; Roy Curtiss, III, et al., 424/235.1, 258.1; 435/172.3, 252.3, 252.33, 320.1, 879; 935/60, 62, 72 [IMAGE AVAILABLE]

6. 5,385,911, Jan. 31, 1995, Anti-herpes castanospermine esters; Sai P. Sunkara, et al., 514/299, 934; 546/112, 138, 183 [IMAGE AVAILABLE]

7. 5,384,122, Jan. 24, 1995, Herpesvirus particles and vaccine; Charles Cunningham, et al., 424/231.1; 435/172.1, 235.1; 530/350 [IMAGE AVAILABLE]

8. 5,383,862, Jan. 24, 1995, Method and device for enveloping and disinfecting of sharp instruments; Dieter R. Berndt, et al., 604/187; 206/365; 604/263 [IMAGE AVAILABLE]

9. 5,380,830, Jan. 10, 1995, Molecular clones of bovine immunodeficiency-like virus; Matthew A. Gonda, 536/23.1; 435/235.1, 236, 320.1; 536/23.72; 935/6, 9, 19, 32 [IMAGE AVAILABLE]

10. 5,378,806, Jan. 3, 1995, Fusion protein produced by retrovirus-mediated secretion; John W. Willis, 530/350; 435/69.7; 530/412; 536/23.4 [IMAGE AVAILABLE]

=> d 11-20

11. 5,378,805, Jan. 3, 1995, Immunoreactive HTLV-I/II ENV and POL peptides; Renu B. Lal, 530/326; 424/187.1; 530/826; 930/10, 220 [IMAGE AVAILABLE]

12. 5,378,603, Jan. 3, 1995, Method and composition for identifying substances which activate transcription of the LDL receptor gene; Michael S. Brown, et al., 435/6, 4, 29, 172.3; 436/817; 935/76, 79, 82 [IMAGE AVAILABLE]

13. 5,377,283, Dec. 27, 1994, Configuration control of mode coupling errors; James N. Blake, et al., 385/11; 250/227.17; 356/350; 385/12 [IMAGE AVAILABLE]

14. 5,376,542, Dec. 27, 1994, Method for producing immortalized cell lines using human papilluma virus genes; Richard Schlegal, 435/172.2, 172.3, 240.1, 240.2; 935/62, 71, 93 [IMAGE AVAILABLE]

15. 5,374,551, Dec. 20, 1994, Methods for detection, identification and speciation of members of the genus Listeria; Barry R. Bochner, 435/252.1, 4, 29, 34, 244 [IMAGE AVAILABLE]

16. 5,374,548, Dec. 20, 1994, Methods and compositions for the attachment of proteins to liposomes using a glycophospholipid anchor; Ingrid W. Caras, 424/450; 435/69.7; 436/829 [IMAGE AVAILABLE]

17. 5,374,519, Dec. 20, 1994, Oligopeptides comprising p18 protein of human immunodeficiency virus (**HIV**), compositions comprising peptides of p18 protein of **HIV**, and diagnostic kits and methods for detecting acquired immune deficiency syndrome (**AIDS**); Luc Montagnier, et al., 435/5, 7.1, 7.2, 7.9, 7.91, 7.92, 7.93, 7.94, 7.95, 974; 530/350 [IMAGE AVAILABLE]

18. 5,374,387, Dec. 20, 1994, Process for processing elastomeric compositions; Roger P. Barnes, et al., 264/211.23, 40.6, 211.24, 349; 425/204 [IMAGE AVAILABLE]

19. 5,371,017, Dec. 6, 1994, Hepatitis C virus protease; Michael Houghton, et al., 435/320.1, 69.1, 69.7; 536/23.2, 23.4, 23.72 [IMAGE AVAILABLE]

20. 5,370,868, Dec. 6, 1994, Therapeutic use of vitaletheine modulators in neoplasia; Galen D. Knight, et al., 424/78.08, 78.37; 514/563 [IMAGE AVAILABLE]

=> d fro 10

US PAT NO: 5,378,806 [IMAGE AVAILABLE] L3: 10 of

5,394 DATE ISSUED: Jan. 3, 1995
TITLE: Fusion protein produced by retrovirus-mediated secretion INVENTOR: John W. Willis, Shreveport, LA
ASSIGNEE: Research Corporation Technologies, Inc., Tucson, AZ (U.S. corp.)
APPL-NO: 07/881,585
DATE FILED: May 12, 1992
REL-US-DATA: Division of Ser. No. 522,428, May 11, 1990, Pat. No. 5,175,099, which is a continuation-in-part of Ser. No. 353,293, May 17, 1989, abandoned.
INT-CL: [6] C07K 13/00
US-CL-ISSUED: 530/350; 435/64.7; 536/23.4; 530/412
US-CL-CURRENT: 530/350; 435/69.7; 530/412; 536/23.4
SEARCH-FLD: 435/64.7; 530/350, 412
REF-CITED:

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| 4,918,166 | 4/1990 | Kingsman et al. | 530/350 |

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ART-UNIT: 182
PRIM-EXMR: Robert J. Hill, Jr.
ASST-EXMR: John D. Ulm
LEGAL-REP: Scully, Scott, Murphy & Presser

ABSTRACT:
The present invention is directed to replicable **expression** vectors for producing fusion proteins which are secreted in membraneous particles budded from the cell membrane. In particular these vectors **express** a hybrid gene product composed of a modified retrovirus **gag** gene fused to a heterologous gene, or any part thereof, wherein the **gag** gene modification is sufficient to enable a cell to produce the hybrid gene product in a membraneous particle by budding from the cell membrane into the culture medium or extracellular space, a process known as retrovirus-mediated secretion. The minimum **gag** sequences needed to obtain particle formation are described. The invention also provides hosts containing the **expression** vectors, and the fusion proteins produced by the vectors. Further the invention provides the membraneous particles produced by retrovirus-mediated secretion and uses of these particles for protein purification and in therapeutics.
7 Claims, 20 Drawing Figures

=> d fro 11

US PAT NO: 5,378,805 [IMAGE AVAILABLE] L3: 11 of 594 DATE ISSUED: Jan. 3, 1995
TITLE: Immunoreactive HTLV-I/II ENV and POL peptides
INVENTOR: Renu B. Lal, Atlanta, GA
ASSIGNEE: United States of America, Washington, DC (U.S. govt.) APPL-NO: 07/574,352
DATE FILED: Aug. 29, 1990
INT-CL: [6] C07K 7/08
US-CL-ISSUED: 530/326; 930/10, 220; 424/187.1; 530/826
US-CL-CURRENT: 530/326; 424/187.1; 530/826; 930/10, 220
SEARCH-FLD: 424/89; 530/324, 325, 326, 826; 430/10, 220
REF-CITED:

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WO90/08162 7/1990 World Intellectual Property Organization

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Journal of Immunology, T. Copeland et al., "Envelope Proteins of Human . . . ", vol. 137, pp. 2945-2951, No. 9, Nov. 1986.
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Palker et al., J. of Immunology 142:971-978, Feb. 1, 1989.
ART-UNIT: 184
PRIM-EXMR: Stephen G. Walsh
LEGAL-REP: Needle & Rosenberg

ABSTRACT:
The present invention relates a peptide having specific immunoreactivity to antibodies to HTLV-I, HTLV-II, or combinations thereof comprising a peptide selected from the group consisting of:
Env-1 (HTLV-I; a.a 191-214)LPHSNLDHILEPSIPWKSKLLTLV,
Env-2 (HTLV-II; a.a 187-210)VHDSDLEHVLTPSTSWTTKILKFI,
Env-5 (HTLV-I; a.a 242-257)SPNVSVPSSSSTPLLY,
Gag-1a (HTLV-I; a.a 102-117)PPSSPTHDPPDSDPQI,
Pol-3 (HTLV-I; a.a 487-502)KQILSQRSFPLPPPHK, and
analogues thereof, wherein the amino acids in the sequence may be substituted as long as the immunoreactivity to antibodies to HTLV-I or HTLV-II derived from the three dimensional conformation of the sequences is substantially preserved.
The invention is further directed to an immunoassay method for the detection of antibodies to HTLV-I, HTLV-II or a combination thereof, a test kit for the detection of said antibodies, a peptide composition containing said peptides and a vaccine.
2 Claims, 7 Drawing Figures

=> d 21-30

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22. 5,366,738, Nov. 22, 1994, Controlled release drug dispersion delivery device; Gerald S. Rork, et al., 424/473, 479, 480, 489 [IMAGE AVAILABLE]

23. 5,364,933, Nov. 15, 1994, Methods of immunopurification of antigens of human immunodeficiency virus type 2 (**HIV**-2); Luc Montagnier, et al., 530/412; 435/235.1, 239, 974; 530/826 [IMAGE AVAILABLE]

24. 5,362,646, Nov. 8, 1994, Expression control sequences; Hermann Bujard, et al., 435/252.33, 69.1, 172.3, 320.1; 536/24.1; 935/29, 41, 43, 73 [IMAGE AVAILABLE]

25. 5,359,046, Oct. 25, 1994, Chimeric chains for receptor-associated signal transduction pathways; Daniel J. Capon, et al., 536/23.4; 435/6, 69.1, 70.2, 235.1, 240.1, 240.2, 320.1; 530/350; 536/23.1, 23.5, 23.51, 23.52, 23.53 [IMAGE AVAILABLE]

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28. 5,358,932, Oct. 25, 1994, Hybrid protein C; Donald C. Foster, et al., 514/12; 435/69.6; 530/380 [IMAGE AVAILABLE]

29. 5,358,866, Oct. 25, 1994, Cytosine deaminase negative selection system for gene transfer techniques and therapies; Craig A. Mullen, et al., 435/240.2, 69.1, 70.1, 227, 240.1, 252.3, 320.1; 536/22.1, 23.1, 23.2, 23.7, 23.74 [IMAGE AVAILABLE]

30. 5,357,636, Oct. 25, 1994, Flexible protective medical gloves and methods for their use; Karl P. Dresdner, Jr., et al., 2/161.7, 167, 168, 169 [IMAGE AVAILABLE]

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=> s mammlian(p)vector?
            17 MAMMLIAN
         44330 VECTOR?
L4            2 MAMMLIAN(P)VECTOR?

=> s mammalian(p)vector?
         13055 MAMMALIAN
         44330 VECTOR?
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L5 1085 MAMMALIAN(P)VECTOR?

=> s (l4 or l5) and l3
L6 100 (L4 OR L5) AND L3

=> d 1-10

1. 5,378,806, Jan. 3, 1995, Fusion protein produced by retrovirus-mediated secretion; John W. Willis, 530/350; 435/69.7; 530/412; 536/23.4 [IMAGE AVAILABLE]

2. 5,378,603, Jan. 3, 1995, Method and composition for identifying substances which activate transcription of the LDL receptor gene; Michael S. Brown, et al., 435/6, 4, 29, 172.3; 436/817; 935/76, 79, 82 [IMAGE AVAILABLE]

3. 5,374,548, Dec. 20, 1994, Methods and compositions for the attachment of proteins to liposomes using a glycophospholipid anchor; Ingrid W. Caras, 424/450; 435/69.7; 436/829 [IMAGE AVAILABLE]

4. 5,374,519, Dec. 20, 1994, Oligopeptides comprising p18 protein of human immunodeficiency virus (**HIV**), compositions comprising peptides of p18 protein of **HIV**, and diagnostic kits and methods for detecting acquired immune deficiency syndrome (**AIDS**); Luc Montagnier, et al., 435/5, 7.1, 7.2, 7.9, 7.91, 7.92, 7.93, 7.94, 7.95, 974; 530/350 [IMAGE AVAILABLE]

5. 5,371,017, Dec. 6, 1994, Hepatitis C virus protease; Michael Houghton, et al., 435/320.1, 69.1, 69.7; 536/23.2, 23.4, 23.72 [IMAGE AVAILABLE]

6. 5,359,046, Oct. 25, 1994, Chimeric chains for receptor-associated signal transduction pathways; Daniel J. Capon, et al., 536/23.4; 435/6, 69.1, 70.2, 235.1, 240.1, 240.2, 320.1; 530/350; 536/23.1, 23.5, 23.51, 23.52, 23.53 [IMAGE AVAILABLE]

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8. 5,358,932, Oct. 25, 1994, Hybrid protein C; Donald C. Foster, et al., 514/12; 435/69.6; 530/380 [IMAGE AVAILABLE]

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US PAT NO: 5,169,763 [IMAGE AVAILABLE] L6: 56 of 100 TITLE: Viral vector coding glycoprotein of **HIV**-1

ABSTRACT:
A viral vector comprising at least a portion of the genome of the **HIV** virus, a gene coding **gp160** glycoprotein of the **envelope** of the **HIV** virus, as well as the elements providing for the **expression** of the glycoprotein in cells, wherein the **gp160** is **expressed** as a non-cleavable protein.

SUMMARY:

BSUM(1)

The present invention relates more especially to a vaccine designed for the prevention of **AIDS**.

SUMMARY:

BSUM(2)

The acquired immune deficiency syndrome (**AIDS**) is a viral condition which is now of major importance in North America, Europe and Central Africa.

SUMMARY:

BSUM(3)

Recent estimates suggest that approximately 1 million Americans may have been exposed to the **AIDS** virus. The affected individuals show severe immunosuppression and the disease is generally fatal.

SUMMARY:

BSUM(6)

Whereas . . . II have been implicated as the causal agent of certain T cell leukemias in adults, the retrovirus associated with lymphadenopathies (**LAV** virus), which is also known as **HTLV** **III** or **AIDS**-related virus (ARV), is now generally accepted as the agent responsible for **AIDS**.

SUMMARY:

BSUM(7)

The genome of the **LAV** retrovirus has been characterized very completely (Wain-Hobson et al., 1985; Ratner et al., 1985; Muesing et al., 1985; Sanchez Pescador. . . the prototype of which is ovine Visna virus, are slowly progressing disease

agents which typically show a prolonged incubation period. **LAV** and Visna virus share many similarities, especially in their tropism for nerve tissue.
SUMMARY:

BSUM(8)

As with other well known retroviruses, the three most important parts of the **LAV** genome have been designated gag, pol and env. The sequence of the env gene, including the sequence of the gp110. . .
SUMMARY:

BSUM(9)

Antibodies . . . env protein gp160 and its cleavage products gp120 and gp41 are commonly detected in the serum of patients who have **AIDS**, and the env glycoprotein represents the major surface antigen of the **AIDS** virus.

SUMMARY:

BSUM(11)

A large number of groups have reported the **expression** of the **env** protein in bacteria. However, the absence of glycosylation and post-translational structuring can impair the immunogenic power of the materials synthesized. . .

SUMMARY:

BSUM(12)

For this reason, the present invention proposes using a viral vector as **expression** vector for the **env** protein, this viral vector enabling the protein to be **expressed** in an **environment** which will permit its glycosylation and its post-translational restructuring.
SUMMARY:

BSUM(13)

Thus, . . . invention relates to a viral vector which contains all or part of the env gene of the virus responsible for **AIDS**.
SUMMARY:

BSUM(23)
a gene coding for one of the glycoproteins (gp) of the envelope of the virus responsible for **AIDS**, and also

SUMMARY:

BSUM(26)

It is appropriate to point out that 3 glycoproteins (gp) may be counted in the envelope of the virus responsible for **AIDS**, designated by their mass in kD, namely the gp160, the gp120 and the gp41; the first, gp160, is, in fact,. . .

SUMMARY:

BSUM(27)

Virus responsible for **AIDS** is understood, in particular, to designate the **LAV** virus, the **HTLV** **III** virus or ARV, and likewise possible point mutants or partial deletions of these viruses, as well as the related viruses.

SUMMARY:

BSUM(28)

In the part corresponding to the genome of the vector virus (as distinct from the virus responsible for **AIDS**), the viral vectors can be formed from the genome of a virus of any origin. However, it is preferable to. . .

SUMMARY:

BSUM(30)

In general, to be capable of being **expressed**, the gene in question, for example the **env** gene, will have to be under the dependence of a promoter of a vaccinia gene; this promoter will generally be. . .
SUMMARY:

BSUM(31)

Among the glycoproteins of the **envelope** whose **expression** it is desired to achieve, the three proteins referred to above, namely the **gp160**, the **gp41** and the **gp120**, should be mentioned.
SUMMARY:

BSUM(32)

In general, it will be preferable to achieve **expression** of the complete **envelope** gene, that is to say the **env** gene incorporating the signal sequence and the transmembrane sequence of this gene.

SUMMARY:

BSUM(33)

As a result of the first tests performed with a viral vector in which the gene coding for the total **env** protein was cloned, modifications of this gene were proposed in order to improve the immunogenicity of the **expression** products.

SUMMARY:

BSUM(51)

The signal peptide and the transmembrane sequence can be those of the virus responsible for **AIDS** or can be heterologous, in particular can originate from the rabies virus or VSV or any virus having an envelope.
SUMMARY:

BSUM(53)

The first (sic) invention relates mainly to the use of viral **vectors** for obtaining the glycoproteins encoded by the env gene of **LAV** virus in cell cultures. The cells in question are hence initially **mammalian** cells which have been infected by a viral **vector** according to the invention, or alternatively which may contain the corresponding recombinant DNA; among these cells, there should be mentioned,. . .
SUMMARY:

BSUM(56)

It . . . combined use of several vaccinating agents, administered jointly or separately, especially the vaccinating agents corresponding to the vectors which separately **express** the **gp120** and the gp40 subjected to the modification described above. For example, it may be advantageous to use jointly the vaccinating. . .

DETDESC:

DETD(3)

FIG. . . . the action of endo-F on the proteins synthesized by the recombinants VVTGeLAV9.sup.-1 and VVTGeLAV1132 and immunoprecipitated by means of an anti-**LAV** serum. In this figure, the molecular weights are given in kilodaltons and the labeling is as follows:

DETDESC:

DETD(8)

FIG. 2 shows the recognition of the proteins of the **LAV** virus by the sera of mice vaccinated with the recombinant VVTGeLAV9-1. In this figure, T denotes the cases where the. . .

DETDESC:

DETD(35)

After immunoprecipitation of the labeled proteins with a serum of a patientsuffering from **AIDS**, the protein A-sepharose fraction is taken up in:

DETDESC:

DETD(44)

**LAV**

DETDESC:

DETD(47)

Plates . . . The mouse sera are then adsorbed onto the plates and the remainder of the procedure is performed as for the **LAV** ELISA.

DETDESC:

DETD(51)

The combined sizes of the different elements required for the transfer of the sequence coding for (sic) the **env** gene into the VV genome, and its subsequent **expression** are of the order of several kb. It was hence considered necessary to reduce to the minimum the size of. . .

DETDESC:

DETD(68)

Plasmids PJ19-13 and PJ 19-6 contain HindIII fragments of the proviral genome of **LAV**, comprising nucleotides 1258 to 1698 and 1698 to 9173, respectively.

DETDESC:

DETD(71)

The introduction of these two PstI restriction sites permits easier manipulation of the DNA of the **env** gene in the

subsequent stages of the construction. As stated above, the **expression** of a heterologous protein invaccinia virus requires that the coding sequence be aligned with a promotersequence of vaccinia and be. . .

DETDESC:

DETD(78)

Cloning into Vaccinia Virus to Generate VV.TG.e **LAV** 9-1
DETDESC:

DETD(85)

The . . . 3.85-, 2.9- and 0.8-kb bands are visible on the autoradiograph when the vaccinia virus has incorporated the env gene of **LAV**. One of these recombinants, VV.TG. eLAV 9-1 was selected for the following studies.

DETDESC:

DETD(87)

Env Protein Synthesized from a Recombinant Vaccinia-**LAV** Virus
DETDESC:

DETD(88)

To demonstrate the **expression** of the **env** gene of **LAV** from the hybrid vaccinia virus, rodent cells, BHK21, which are cultured in a G-MEM medium +10% of fetal calf serum. . .

DETDESC:

DETD(90)

The . . . by centrifugation. After separationinto pellet and supernatant, the proteins are incubated with a serum belonging to a patient suffering from **AIDS**. The proteins which react with the serum are recovered by adsorption on a protein A-Sepharose resin, and spread by electrophoresis. . . according to a technique described by Lathe et al., 1980.The autoradiographs show that the serum of the patient suffering from **AIDS** specifically binds three proteins in the infected cell extracts (the result is identical or similar to that obtained with other sera of patients). The apparent molecular weights of 160, 120 and 41 kD suggest equivalence with the **gp160**, **gp120** and gp 41 bands identified by means of sera

of patients suffering from **AIDS** in an authentic **env** glycoprotein preparation and in extracts of cells infected with the **LAV** virus. This observation, that three proteins are **expressed** from the recombinant vectorwhich carries only the sequence coding for (sic) the **env** gene of **LAV**, supports the hypothesis that the **gp120** and **gp41** are generated by proteolytic cleavage of the primary translation product, **gp160**.

DETDESC:

DETD(93)

Demonstration of Anti-env Antibodies in Mice Vaccinated with the VV.TG.e **LAV** 9-1 Virus

DETDESC:

DETD(94)

5-week-old male Balb/c mice are vaccinated by subcutaneous injection of 5.times.10.sup.7 pfu of VV.TV.e **LAV** 9-1 virus per animal. They receive a booster injection with the same dose after 2 weeks, and blood samples are withdrawn 1, 2 and 4 weeks after the booster. The presence of antibodies directed against determinants of **LAV** virus and of vaccinia virus in their sera is sought.

DETDESC:

DETD(95)

All . . . sera capable of reacting with vaccinia virus in an ELISA test. In contrast, the response in the ELISA test against **LAV** virus is weak and of low reproducibility. To improve the sensitivity of the tests, a "Western blot" technique was used. This methodenables antibodies capable of reacting with the proteins of **LAV** virus to bedemonstrated after these proteins have been denatured with SDS in an electrophoresis gel and transferred to a nitrocellulose membrane. In this experiment, the nitrocellulose membranes employed are those of the **LAV**-BLOT kit sold by Diagnostic-Pasteur and to which the proteins of **LAV** virus are already bound. These membranes are cut into strips and each strip is incubated with the serum of the vaccinated mice (1/20 dilution). A second antibody (sheep anti-mouse) linked to peroxydase enables the proteins of the **LAV** virus which have bound mouse antibodies to be visualized.
DETDESC:

DETD(96)

Several . . . be noted that the sera of a few mice produce signals in Western blot corresponding to unidentified proteins of the **LAV** virus preparation bound to the membranes.

DETDESC:

DETD(177)

The kinetics of release performed on the VV.TG. eLAV1133 and 1134 viruses show that, although the kinetics of cutting between the **gp120** and the gp40are slower, the cleavage still takes place. The examination of the DNA sequence of the **env** gene reveals another potential cleavage site (KRR) 8 amino acids downstream from the first cleavage site. It may hence be important to mutate this second site so as to obtain a recombinant vaccinia virus which **expresses** only the **gp160**.

DETDESC:

DETD(184)

The . . . have another recombinant in which this C-terminal portion was replaced by the C-terminal portion of the env gene of the **LAV** virus.

DETDESC:

DETD(189)

It would also be desirable to have a recombinant vaccinia virus which **expressed** only the **gp120**. This gp-120 will, in distinction to the case obtained with the VV.TG.eLAV1132 virus, be equipped with a C-terminal anchorage region.

DETDESC:

DETD(203)

In addition to recombinant viruses which **express** the **gp160** or the **gp120**, itmay be useful to generate a recombinant vaccinia virus which **expresses** the gp40 alone.

DETDESC:

DETD(210)

As in the case of the **gp160** (plasmid pTG1139), it may also be important to have a recombinant virus which **expresses** a gp40 in which the anchorage region and the intracytoplasmic

region are the sequences of the **env** gene of the **LAV** virus, rather than the corresponding sequences of the rabies glycoprotein.

DETDESC:

DETD(240)
10. . . . D., Benton, C. V., Lasky, L. A. and Capon, D. J. 1985. Nucleic acid structure and expression of the human **AIDS**/lymphadenopathy retrovirus. Nature 313 : 450-458.
DETDESC:

DETD(244)
14. . . . J. A., Papas, T. S., Ghrayeb, J., Chang, N. T., Gallo, R. C.and Wong-Staal, F. Complete nucleotide sequence of the **AIDS** virus, **HTLV**-**III**. 1985. Nature 313 : 277-284.

DETDESC:

DETD(249)
19. Wain-Hobson, S., Sonigo, P., Danos, O., Cole, S. and Alizon, M. Nucleotide Sequence of the **AIDS** virus, **LAV**. 1985. Cell 40 : 9-17.

CLAIMS:

CLMS(1)

We claim:

1. A viral **vector**, the genome of which comprises:
a functional origin of replication of a poxvirus;
a first DNA fragment encoding a non-cleavable **gp160**, consisting of **gp120**-gp140, derived from the natural **gp160** of an **HIV**-1 virus, said non-cleavable **gp160** being characterized in that it does not contain the amino acid sequence REKR originally found in the natural **gp160**;
a second DNA fragment encoding a signal peptide, said second DNA fragment being linked to the 5' end of said first DNA fragment; and a promoter for **expressing** said DNA fragment in **mammalian** cells.
CLAIMS:

CLMS(2)

2. . . . the genome of which comprises a first DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being characterized in that it does not contain the amino acid sequences KRR and REKR originally. . .

CLAIMS:

CLMS(3)

3. . . . the genome of which comprises a first DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being characterized in that it comprises a 4-amino acid sequence other than REKR in place of. . .
CLAIMS:

CLMS(4)

4. . . . the genome of which comprises a first DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being characterized in that it comprises a 4-amino acid sequence other than REKR in place of. . .
CLAIMS:

CLMS(5)

5. . . . 3, the genome of which comprises a DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being different from the natural gp160 in that the amino acid sequence REKR originally found in. . .
CLAIMS:

CLMS(6)

6. . . . 4, the genome of which comprises a DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being different from the natural gp160 in that the amino acid sequences KRR and REKR are. . .

CLAIMS:

CLMS(7)

7. . . . of which comprises a first DNA fragment encoding a non-cleavable and soluble gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable and soluble gp160 being different from the natural gp160 in that it does not contain the amino. . .
CLAIMS:

CLMS(10)

10. . . . of which comprises a first DNA fragment encoding a

non-cleavable and soluble gp160 derived form the natural gp160 of the **HIV**-1 virus, said non-cleavable and soluble gp160 being different from the natural gp160 in that it does not contain the amino. . .
CLAIMS:

CLMS(13)

13. . . . the genome of which comprises a first DNA fragment encoding a non-cleavable gp160 derived form the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being characterized in that it does not contain the amino acid sequence REKR originally found in. . .
CLAIMS:

CLMS(15)

15. . . . the genome of which comprises a first DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being characterized in that it does not contain the amino acid sequences KRR and REKR originally. . .
CLAIMS:

CLMS(17)

17. . . . the genome of which comprises a first DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being characterized in that it does not contain the amino acid sequence REKR originally found in. . .
CLAIMS:

CLMS(19)

19. . . . the genome of which comprises a first DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being characterized in that it does not contain the amino acid sequences KRR and REKR originally. . .
CLAIMS:

CLMS(21)

21. . . . the genome of which comprises a first DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being characterized in that it does not contain the amino acid sequence REKR originally found in. . .
CLAIMS:

CLMS(22)

22. . . . the genome of which comprises a first DNA fragment encoding a non-cleavable gp160 derived from the natural gp160 of the **HIV**-1 virus, said non-cleavable gp160 being characterized in that it does not contain the amino acid sequences REKR and KRR originally. . .
CLAIMS:

CLMS(23)

23. . . . peptide which is selected from the group consisting of the signal peptide of the precursor of the gp160 of the **HIV**-1 virus and the signal peptide of the precursor of the glycoprotein of the rabies virus.

CLAIMS:

CLMS(24)

24. . . . peptide which is selected from the group consisting of the signal peptide of the precursor of the gp160 of the **HIV**-1 virus and the signal peptide of the precursor of the glycoprotein of the rabies virus.

CLAIMS:

CLMS(29)

29. A viral vector according to claim 1, wherein the DNA encoding envelope protein of **HIV**-1 is encoded by the EcoRI-KpnI and KpnI-HindIII fragments of plasmid PJ19-13, comprising nucleotides 1258 to 1698 of the DNA encoding envelope protein of **HIV**-1, and the HindIII-XhoI fragment of plasmid PJ19-6, comprising nucleotides 1698 to 9173 of the DNA encoding envelope protein of **HIV**-1.

CLAIMS:

CLMS(30)

30. A viral vector according to claim 2, wherein the DNA encoding envelope protein of **HIV**-1 is encoded by the EcoRI-KpnI and KpnI-HindIII fragments of plasmid PJ19-13, comprising nucleotides 1258 to 1698 of the DNA encoding envelope protein of **HIV**-1, and the HindIII-XhoI fragment of plasmid PJ19-6, comprising nucleotides 1698 to 9173 of the DNA encoding envelope protein of **HIV**-1.

CLAIMS:

CLMS(31)

31. A culture of **mammalian** cells, which is infected with a viral **vector** as claimed in any one of claims 1 to 6 or 13 to 28.
CLAIMS:

CLMS(32)

32. A culture of **mammalian** cells, which is infected with a viral **vector** as claimed in any one of claims 7 to 12.

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US PAT NO: 5,169,763 [IMAGE AVAILABLE] L6: 56 of 100 DATE ISSUED: Dec. 8, 1992
TITLE: Viral vector coding glycoprotein of **HIV**-1
INVENTOR: Marie-Paule Kieny, Strasbourg, France
Guy Rautmann, Strasbourg, France
Jean-Pierre Lecocq, Reichstett, France
Simon W. Hobson, Montigny-le-Bretonneux, France
Marc Girard, Paris, France
Luc Montagnier, Le Plessis-Robinson, France
ASSIGNEE: Transgene S.A., Institut Pasteur, France (foreign corp.) APPL-NO: 07/765,413
DATE FILED: Sep. 24, 1991
REL-US-DATA: Continuation of Ser. No. 143,079, Dec. 4, 1987, abandoned. FRN-PRIOR: France 86 05043
Apr. 8, 1986 France 86 15106
Oct. 29, 1986 INT-CL: [5] C12N 15/49; C12N 15/86; C12N 5/10; C12P 21/02 US-CL-ISSUED: 435/69.3, 5, 69.1, 69.7, 172.3, 240.2, 974, 320.1; 530/395; 930/221; 935/32, 34, 70
US-CL-CURRENT: 435/69.3, 5, 69.1, 69.7, 172.3, 240.2, 320.1, 974; 530/395; 930/221; 935/32, 34, 70
SEARCH-FLD: 435/69.1, 69.3, 69.7, 240.2, 320.1; 530/395
REF-CITED:

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ART-UNIT: 185
PRIM-EXMR: Richard A. Schwartz
ASST-EXMR: Johnny F. Railey, II
LEGAL-REP: Finnegan, Henderson, Farabow, Garrett & Dunner
ABSTRACT:
A viral vector comprising at least a portion of the genome of the **HIV** virus, a gene coding **gp160** glycoprotein of the **envelope** of the **HIV** virus, as well as the elements providing for the **expression** of the glycoprotein in cells, wherein the **gp160** is **expressed** as a non-cleavable protein.
33 Claims, 5 Drawing Figures

=> d fro 58

US PAT NO: 5,166,050 [IMAGE AVAILABLE] L6: 58 of 100 DATE ISSUED: Nov. 24, 1992
TITLE: Monoclonal antibodies and peptides useful in treating and diagnosing **HIV** infections
INVENTOR: Mary K. Shriver, Bellevue, WA
Larry H. Gosting, Snohomish, WA
Edna S. Dickinson, Seattle, WA
Janela McClure, City of Vashon Is., WA
Elaine K. Thomas, Seattle, WA
Wesley L. Cosand, Bothell, WA
ASSIGNEE: Bristol-Myers Squibb Company, New York, NY (U.S. corp.) APPL-NO: 07/625,777
DATE FILED: Dec. 7, 1990
REL-US-DATA: Continuation of Ser. No. 547,428, Jul. 3, 1990, abandoned, which is a continuation of Ser. No. 45,026, May 1, 1987, abandoned, which is a continuation-in-part of Ser. No. 898,273, Aug. 20, 1986, abandoned.
INT-CL: [5] G01N 33/569; C12N 5/20; C07K 15/28; A61K

39/42 US-CL-ISSUED: 435/5, 70.21, 172.2, 240.27; 530/388.1, 388.35, 389.4, 864, 868; 424/85.8, 86
US-CL-CURRENT: 435/5; 424/139.1, 148.1, 188.1, 208.1; 435/70.21, 172.2, 240.27; 530/388.1, 388.35, 389.4, 864, 868 SEARCH-FLD: 435/70.21, 172.2, 240.27, 5; 530/388.1, 388.35, 389.4; 424/85.8, 86, 89
REF-CITED:

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| 251612 | 1/1988 | European Patent Office | |
| 255190 | 2/1988 | European Patent Office | |
| 273716 | 7/1988 | European Patent Office | |
| 2188639A | 10/1987 | United Kingdom | |
| 86/02383 | 4/1986 | World Intellectual Property Organization | |
| 86/04336 | 7/1986 | World Intellectual Property Organization | |
| 86/04613 | 8/1986 | World Intellectual Property Organization | 435/5 |
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ART-UNIT: 186
PRIM-EXMR: John J. Doll
ASST-EXMR: Robert D. Budens
LEGAL-REP: Townsend and Townsend

ABSTRACT:
Methods and composition for **HIV** diagnosis and treatment using monoclonal antibodies reactive with one or more neutralizing regions of **HIV** proteins, using the peptides or homologs thereof from that region, and using related nucleic acid segments. Exemplary neutralizing regions include selected portions of the env and gag genes from various **HIV** isolates. Monoclonal antibody secreting cell lines include **HIV**-gp110-1, -2, -3, -4, -5 and -6 (A.T.C.C. Accession Nos. HB9175, HB9176, HB9177, HV9405, HB9406 and HB9404, respectively) and **HIV**-p25-2, -3, -6 and -7 (A.T.C.C. Accession Nos. HB9407, HB9408, HB9409 and HB9410, respectively).
17 Claims, No Drawings

=> d fro 68

US PAT NO: 5,130,248 [IMAGE AVAILABLE] L6: 68 of 100
DATE ISSUED: Jul. 14, 1992
TITLE: **Expression** of fusion protein of **HIV** **envelope** and HBsAg
INVENTOR: Peter J. Kniskern, Lansdale, PA
Arpi Hagopian, Lansdale, PA

Pamela Burke, Lansdale, PA
ASSIGNEE: Merck & Co., Inc., Rahway, NJ (U.S. corp.)
APPL-NO: 07/409,190
DATE FILED: Sep. 19, 1989
INT-CL: [5] C12N 5/06; C12N 5/19; C12P 21/06; C07H 21/04
US-CL-ISSUED: 435/240.2, 172.3, 69.1, 69.3, 320.1, 255; 536/27; 935/10, 22
US-CL-CURRENT: 435/240.2, 69.1, 69.3, 172.3, 254.2, 320.1; 536/23.4, 23.72; 935/10, 22
SEARCH-FLD: 536/27; 435/172.3, 69.9, 240.2, 320.1, 255, 256
REF-CITED:

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| 0322394 | 6/1989 | European Patent Office |

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ABSTRACT:
The present invention relates to recombinant fusion polypeptides of **HIV** envelope and HBsAg, suitable as vaccines against **AIDS** and/or ARC and hepatitis, as well as immunogens for inducing antibodies for passive protection or treatment of **AIDS** and/or ARC.
4 Claims, No Drawings

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TITLE: Variant of **LAV** viruses
INVENTOR: Marc Alizon, Paris, France
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Science, 227 (1985) 484-492.
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ABSTRACT:

A variant of a **LAV** virus, designated **LAV**.sub.ELI and capable of causing **AIDS**. The cDNA and antigens of the **LAV**.sub.ELI virus can be used for the diagnosis of **AIDS** and pre-**AIDS**.

9 Claims, 7 Drawing Figures

=> d kwic 82

US PAT NO: 5,034,511 [IMAGE AVAILABLE] L6: 82 of 100 TITLE: Variant of **LAV** viruses

ABSTRACT:
A variant of a **LAV** virus, designated **LAV**.sub.ELI and capable of causing **AIDS**. The cDNA and antigens of the **LAV**.sub.ELI virus can be used for the diagnosis of **AIDS** and pre-**AIDS**.

SUMMARY:

BSUM(2)

The present invention relates to a virus capable of inducing lymphadenopathies (hereinafter "LAS") and acquired immuno-depressive syndromes (hereinafter "**AIDS**"), to antigens of this virus, particularly in a purified form, and to a process for producing these antigens, particularly antigens. . . . The invention further relates to cloned DNA sequences hybridizable to genomic RNA and DNA of the lymphadenopathy associated virus (hereinafter "**LAV**") of this invention and to processes for their preparation and their use. The invention still further relates to a stable probe including a DNA sequence which can be used for the detection of the **LAV** virus of this invention or related viruses or DNA proviruses in any medium, particularly biological, and in samples containing any. . .

SUMMARY:

BSUM(3)

An important genetic polymorphism has been recognized for the human retrovirus which is the cause of **AIDS** and other diseases like LAS, **AIDS**-related complex (hereinafter "ARC") and probably some encephalopathies (for review, see Weiss, 1984). Indeed all of the isolates, analyzed until now,. . . time [Benn et al., 1985]. Identical restriction maps have only been observed for the first two isolates which were designated **LAV** [Alizon et al., 1984] and human T-cell lymphotropic virus type 3 (hereinafter "HTLV-3") [Hahn et al., 1984] and which appear to be exceptions. The genetic polymorphism of the **AIDS** virus was better assessed after the determination of the complete nucleotide sequence of **LAV** [Wain-Hobson et al.,

1985], HTLV-3 [Ratner et al., 1985; Muesing et al., 1985] and a third isolate designated **AIDS**-associated retrovirus (hereinafter "ARV 2") [Sanchez-Pescador et al., 1985]. In particular, it appeared that, besides the nucleic acid variations responsible for. . . isolates could differ significantly at the protein level, especially in the envelope (up to 13% of difference between ARV and **LAV**), by both amino acids substitutions and reciprocal insertions-deletions [Rabson and Martin, 1985].
SUMMARY:

BSUM(4)

Nevertheless, . . . or similar envelope glycoproteins, such as the 110-120 kD glycoproteins) to immunologically cross-react. Accordingly, the proteins of any of said **LAV** viruses can be used for the in vitro detection of antibodies induced in vivo and present in biological fluids obtained from individuals infected with the other **LAV** variants. Therefore, these viruses are grouped together as a class of **LAV** viruses (hereinafter "**LAV**-1 viruses").

SUMMARY:

BSUM(6)

In accordance with this invention, a new virus has been discovered that is responsible for diseases clinically related to **AIDS** and that can be classified as a **LAV**-1 virus but that differs genetically from known **LAV**-1 viruses to a much larger extent than the known **LAV**-1 viruses differ from each other. The new virus is basically characterized by the cDNA sequence which is shown in FIGS. 7A to 7I, and this new virus is hereinafter generally referred to as "**LAV**.sub.ELI ".
SUMMARY:

BSUM(7)

Also . . . of these variants and the related cDNAs derived from said RNAs are hybridizable to corresponding parts of the cDNA of **LAV**.sub.ELI. The DNA of the new virus also is provided, as well as DNA fragments derived therefrom hybridizable with the genomic RNA of **LAV**.sub.ELI, such DNA and DNA fragments particularly consisting of the cDNA or cDNA fragments of **LAV**.sub.ELI or of recombinant DNAs containing such cDNA or cDNA fragments.

SUMMARY:

BSUM(8)

'DNA recombinants containing the DNA or DNA fragments of **LAV**.sub.ELI or its variants are also provided. It is of course understood that fragments which would include some deletions or mutations which would not substantially alter their capability of also hybridizing with the retroviral genome of **LAV**.sub.ELI are to be considered as forming obvious equivalents of the DNA or DNA fragments referred to hereinabove.

SUMMARY:

BSUM(9)

Cloned . . . any plasmids amplifiable in procaryotic or eucaryotic cells and carrying said fragments. Using cloned DNA containing a DNA fragment of **LAV**.sub.ELI as a molecular hybridization probe-either by marking with radionucleotides or with fluorescent reagents-**LAV** virion RNA may be detected directly, for example, in blood, body fluids and blood products (e.g., in antihemophylic factors such as Factor VIII concentrates). A suitable method for achieving such detection comprises immobilizing **LAV**.sub.ELI on a support (e.g., a nitrocellulose filter), disrupting the virion and hybridizing with a labelled (radiolabelled or "cold" fluorescent- or. . .

SUMMARY:

BSUM(10)

Probes . . . to the invention can also be used for rapid screening of genomic DNA derived from the tissue of patients with **LAV** related symptoms to see if the proviral DNA or RNA present in their tissues is related to **LAV**.sub.ELI. A method which can be used for such screening comprises the following steps: extraction of DNA from tissue, restriction enzyme. . . said DNA, electrophoresis of the fragments and Southern blotting of genomic DNA from tissues and subsequent hybridization with labelled cloned **LAV** proviral DNA. Hybridazation in situ can also be used. Lymphatic fluids and tissues and other non-lymphatic tissues of humans, primates. . .

SUMMARY:

BSUM(11)

The DNA according to the invention can be used also for achieving the expression of **LAV** viral antigens for diagnostic purposes, as well as for the production of a vaccine against **LAV**. Fragments of particular advantage in that respect will be discussed later. The methods which can be used are multifold:

SUMMARY:

BSUM(13)

b) DNA fragments corresponding to genes can be cloned into expression **vectors** for E. coli, yeast or **mammalian** cells and the resultant proteins purified. PG,6

SUMMARY:

BSUM(15)

Recombinants, producing antigenically competent fusion proteins, can be identified by simply screening the recombinants with antibodies against **LAV**.sub.ELI antigens. Particular reference in this respect is made to those portions of the genome of **LAV**.sub.ELI which, in the figures, are shown to belong to open reading frames and which encode the products having the polypeptidic. . .

SUMMARY:

BSUM(16)

Different . . . 978 and in PCT application PCT/EP 85/00548, filed Oct. 18, 1985, are applicable for the production of such peptides from **LAV**.sub.ELI. In this regard, polypeptides are provided containing sequences in common with polypeptides comprising antigenic determinants included in the proteins encoded and expressed by the **LAV**.sub.ELI genome. Means are also provided for the detection of proteins of **LAV**.sub.ELI, particularly for the diagnosis of **AIDS** or pre-**AIDS** or, to the contrary, for the detection of antibodies against **LAV**.sub.ELI or its proteins, particularly in patients afflicted with **AIDS** or pre-**AIDS** or more generally in asymtomatic carriers and in blood-related products. Further provided are immunogenic polypeptides and more particularly protective polypeptides for use in the preparation of vaccine compositions against **AIDS** or related syndroms.
SUMMARY:

BSUM(18)

Other features of this invention will appear in the following disclosure of data obtained starting from **LAV**.sub.ELI, in relation to the drawings.

DRAWING DESC:

DRWD(2)

FIGS. 1A and 1B provide comparative restriction maps of the genomes of **LAV**.sub.ELI as compared to **LAV**.sub.MAL (Applicants' related new **LAV** virus which is the subject of their copending application, filed herewith) and **LAV**.sub.BRU (a known **LAV** isolate deposited at the Collection Nationale des Cultures de Micro-organismes (hereinafter "CNCM") of the Pasteur Institute, Paris, France under No. . . .
DRAWING DESC:

DRWD(4)

FIGS. . . . correspondance between the proteins (or glycoproteins) encoded by the open reading frames, whereby amino acid residues of protein sequences of **LAV**.sub.ELI are in vertical alignment with corresponding amino acid residues (numbered) of corresponding or homologous proteins or glycoproteins of **LAV**.sub.BRU, as well as **LAV**.sub.MAL and ARV 2;

DRAWING DESC:

DRWD(5)

FIGS. 4A-4B (also designated generally hereinafter "FIG. 4") provide tables quantitating the sequence divergence between homologous proteins of **LAV**.sub.BRU, **LAV**.sub.ELI and **LAV**.sub.MAL ;
DRAWING DESC:

DRWD(7)

FIGS. . . . and 6B ("FIG. 6" when consulted together) render apparent the direct repeats which appear in the proteins of the different **AIDS** virus isolates.

DRAWING DESC:

DRWD(8)

FIGS. 7A-7I show the full nucleotide sequences of **LAV**.sub.ELI.
DETDESC:

DETD(3)

The different **AIDS** virus isolates concerned are designated by three letters of the patients name, **LAV**.sub.BRU referring to the prototype **AIDS** virus isolated in 1983 from a French homosexual patient with LAS and thought to have been infected in the USA in the preceding years [Barre-Sinoussi et al., 1983].

**LAV**.sub.ELI was recovered in 1983 from a 24-year old woman with **AIDS** from Zaire. Related **LAV**.sub.MAL was recovered in 1985 from a 7-year old boy from Zaire. Recovery and purification of the **LAV**.sub.ELI virus were performed according to the method disclosed in European Patent Application 84 401834/138 667 filed on Sept. 9, 1984.

DETDESC:

DETD(4)

**LAV**.sub.ELI is indistinguishable from the previously characterized isolates by its structural and biological properties in vitro. Virus metabolic labelling and immune precipitation by patient ELI sera, as well as reference sera, showed that the proteins of **LAV**.sub.ELI had the same molecular weight (hereinafter "MW") as, and cross-reacted immunologically with those of, prototype **AIDS** virus (data not shown) of the **LAV**-1 class.

DETDESC:

DETD(6)

Primary restriction enzyme analysis of **LAV**.sub.ELI genome was done by southern blot with total DNA derived from acutely infected lymphocytes, using cloned **LAV**.sub.BRU complete genome as probe. Overall cross-hybridization was observed under stringent conditions, but the restriction profile of the Zairian isolate was. . . information were obtained and further characterized by restriction mapping and nucleotide sequence analysis. A Clone (hereinafter "E-H12") was derived from **LAV**.sub.ELI infected cells and contained an integrated provirus with 5' flanking cellular sequences but a truncated 3' long terminal repeat (hereinafter. . .

DETDESC:

DETD(7)

FIG. 1B gives a comparison of the restriction maps derived from the nucleotide sequences of **LAV**.sub.ELI, **LAV**.sub.MAL and prototype **LAV**.sub.BRU, as well as from three other Zairian isolates (hereinafter "Z1", "Z2", and "Z3" respectively) previously mapped for seven restriction enzymes. . . this limited number, all of the profiles are clearly different (out of the 23 sites making up the map of **LAV**.sub.BRU, only seven are present in all six maps presented), confirming the genetic polymorphism of the **AIDS** virus. No obvious relationship is apparent between the five Zairian maps, and all of their common sites are also found in **LAV**.sub.BRU.

DETDESC:

DETD(9)

The genetic organization of **LAV**.sub.ELI as deduced from the complete nucleotide sequences of its cloned genome is identical to that found in other isolates, i.e., 5'**gag**-pol-central region-**env**-F3. Most noticeable is the conservation of the "central region" (FIG. 2), located between the pol and **env** genes, which is composed of a series of overlapping open reading frames (hereinafter "orf") previously designated Q, R, S, T,. . . visna [Sonigo et al., 1985]. The product of orf S (also designated "tat") is implicated in the transactivation of virus **expression** [Sodroski et al., 1985; Arya et al., 1985]; the biological role of the product of orf Q (also designated "sor". . . and finally the fact that the variation of its protein sequence within the different isolates is comparable to that of **gag**, pol and Q (see FIG. 4).

DETDESC:

DETD(11)

Overall, it clearly appears that this Zairian isolate, **LAV**.sub.ELI, is the same type of retrovirus as the previously sequenced isolates of American or European origin.

DETDESC:

DETD(13)

Despite their identical genetic organization, the **LAV**.sub.ELI and **LAV**.sub.MAL shows substantial differences in the primary structure of their proteins. The amino acid sequences of **LAV**.sub.ELI and **LAV**.sub.MAL proteins are presented in FIGS. 3A-3F, aligned with those of **LAV**.sub.BRU and ARV 2. Their divergence was quantified as the percentage of amino acids substitutions in two-by-two alignments (FIG. 4). The. . .

DETDESC:

DETD(14)

Three general observations can be made. First, the protein sequences of the **LAV**.sub.ELI and **LAV**.sub.MAL are more divergent from **LAV**.sub.BRU than are those of HTLV-3 and ARV 2 (FIG. 4A); similar results are obtained if ARV 2 is taken as reference (not shown). The range of genetic polymorphism between isolates of the **AIDS** virus is considerably greater than previously observed. Second, our two sequences confirm that the

envelope is more variable than the gag and pol genes. Here again, the relatively small difference observed between the env of **LAV**.sub.BRU and HTLV-3 appears as an exception. Third, the mutual divergence of the **LAV**.sub.ELI and **LAV**.sub.MAL (FIG. 4B) is comparable to that between **LAV**.sub.BRU and either of them; as far as we can extrapolate from only three sequenced isolates from the USA and Europe and two (**LAV**.sub.ELI and **LAV**.sub.MAL) from Africa, this is indicative of a wider evolution of the **AIDS** virus in Africa.

DETDESC:

DETD(15)

gag . . . structural or enzymatic activities. Of the three mature gag proteins, the p25 which was the first recognized immunogenic protein of **LAV** [Barre-Sinoussi et al., 1983] is also the better conserved (FIG. 3). In gag and pol, differences between isolates are principally. . . deletional events is observed. Among these, we must note the presence in the overlapping part of gag and pol of **LAV**.sub.BRU of an insertion of 12 amino acids (AA) which is encoded by the second copy of a 36 bp direct. . . in this isolate and in HTLV-3. This duplication was omitted because of a computing error in the published sequence of **LAV**.sub.BRU (position 1712, Wain-Hobson et al., 1985) but was indeed present in the HTLV-3 sequences [Ratner et al., 1985; Muesing et. . .
DETDESC:

DETD(17)

From . . . have not included the sequence of the envelope of the HTLV-3 isolate since it is so close to that of **LAV**.sub.BRU (cf. FIG. 4), even in the hypervariable domains, that it did not add anything to the analysis. While this graphical. . .

DETDESC:

DETD(19)

About . . . of the potential N-glycosylation sites, Asn-X-Ser/Thr, found in the envelopes of the Zairian isolates map to the same positions in **LAV**.sub.BRU (17/26 for **LAV**.sub.ELI and 17/28 for **LAV**.sub.MAL). The other sites appear to fall within variable domains of env, suggesting the existence of differences in the extent of. . .
DETDESC:

DETD(20)

'Other . . . no more variable than gag. Also noticeable is the lower variation of the proteins encoded by the central regions of **LAV**.sub.ELI and **LAV**.sub.MAL.

DETDESC:

DETD(21)

With the availability of the complete nucleotide sequence from five independant isolates, some general features of the **AIDS** virus' genetic variability are now emerging. Firstly, its principal cause is point mutations which very often result in amino acid. . .
DETDESC:

DETD(22)

Another . . . of a direct repeat (FIG. 6). Some are perfectly conserved like the 36 bp repeat in the gag-pol overlap of **LAV**.sub.BRU (FIG. 6A-a); others carry point mutations resulting in amino acid substitutions, and as a consequence, they are more difficult to. . . to their date of occurrence in the analyzed sequences: the more degenerated, the more ancient. A very recent divergence of **LAV**.sub.BRU and HTLV-3 is suggested by the extremely low number of mismatched AA between their homologous proteins. However, one of the **LAV**.sub.BRU repeats (located in the Hyl domain of env, FIG. 6B-f) is not present in HTLV-3, indicating that this generation of. . .
DETDESC:

DETD(23)

Genetic . . . or by generating a large repertoire of antigens, as observed in influenza virus [Webster et al., 1982]. As the human **AIDS** virus is related to animal lentiviruses [Sonigo et al., 1985; Chiu et al., 1985], its genetic variability could be a. . . these animal models is the extremely low, and possibly nonexistent, neutralizing activity of the sera of individuals infected by the **AIDS** virus, whether they are healthy carriers, displaying minor symptoms, or afflicted with **AIDS** [Weiss et al., 1985; Clavel et al., 1985]. Furthermore, even for the visna virus the exact role of antigenic variation. . . an adaptation to different environments, for example by modifying their tissue or host tropisms. In the particular case of the **AIDS** virus, rapid genetic variations are tolerated, especially in the envelope. This could allow the virus to become adapted to different. . .

DETDESC:

DETD(24)

Conserved domains in the **AIDS** virus envelope

DETDESC:

DETD(25)

Since . . . differences do not seem to affect the sensitivity of actual diagnostic tests, based upon the detection of antibodies to the **AIDS** virus and using purified virions as antigens. They nevertheless have to be considered for the development of the "second-generation" tests,. . . TMP (490-620, FIG. 3) could be a good candidate, since a bacterial fusion protein containing this domain was well-detected by **AIDS** patients' sera [Chang et al., 1985].

DETDESC:

DETD(26)

The . . . a retrovirus and its specific cellular receptor [DeLarco and Todaro, 1976; Robinson et al., 1980]. In the case of the **AIDS** virus, in vitro binding assays have shown the interaction of the envelope glycoprotein gp110 with the T4 cellular surface antigen. . . thought to be closely associated with the virus receptor [Klatzmann et al., 1984; Dagleish et al., 1984]. Identification of the **AIDS** virus envelope domains that are responsible for this interaction (receptor-binding domains) appears to be fundamental for understanding of the host-viral. . . and for designing a protective vaccine, since an immune response against these epitopes could possibly elicit neutralizing antibodies. As the **AIDS** virus receptor is at least partly formed of a constant structure, the T4 antigen, the binding site of the envelope. . .

DETDESC:

DETD(27)

African **AIDS** viruses

DETDESC:

DETD(28)

Zaire and the neighboring countries of Central Africa are considered as an area endemic with the **AIDS** virus infection, and the possibility that the virus has emerged in Africa has became a subject of intense controversy (see. . .

DETDESC:

DETD(29)

A novel human retrovirus with morphology and biologocal properties (cytopathogenicity, T4 tropism) similar to those of **LAV**, but nevertheless clearly genetically and antigenically distinct from it, was recently isolated from two patients with **AIDS** originating from Guinea Bissau, West-Africa [Clavel et al., 1986]. In neighboring Senegal, the population was seemingly exposed to a retrovirus also distinct from **LAV** but apparently non-pathogenic [Barin et al., 1985; Kanki et al., 1986]. Both of these novel African retroviruses seem to be. . . raises the possibility of a large group of African primate lentiviruses, ranging from the apparently non-pathogenic simian viruses to the **LAV**-type viruses. Their precise relationship will only be known after their complete genetic characterization, but it is already very likely that they have evolved from a common progenitor. The important genetic variability we have observed between isolates of the **AIDS** virus in Central Africa is probably a hallmark of this entire group and may account for the apparently important genetic. . .

DETDESC:

DETD(32)

**LAV**.sub.ELI was isolated from the peripheral blood lymphocytes of the patient as described [Barre-Sinoussi et al., 1983]. Briefly, the lymphocytes were. . .

DETDESC:

DETD(34)

Normal . . . 1982]was constructed by partial HindIII digestion of the DNA as already described [Alizon et al., 1984]. About 5.times.10.sup.5- plaques for **LAV**.sub.ELI, obtained by in vitro packaging (Amersham), were plated on E. coli LA101 and screened in situ under stringent conditions, using the 9 kb SacI insert of the clone lambda J19 [Alizon et al., 1984]carrying most of the **LAV**.sub.BRU genome as probe. Clones displaying positive signals were plaque-purified and propagated on E. coli C600 recBC, and the recombinant phage E-H12 carrying the complete genetic information of **LAV**.sub.ELI was further characterized by restriction mapping.

DETDESC:

DETD(36)

'Viral . . . cloning in the M13mp8 vector [Messing and Viera, 1982] as previously described [Sonigo et al., 1985]. The viral genome of **LAV**.sub.ELI is 9176 nucleotides long as shown in FIGS. 7A-7I. Each nucleotide of **LAV**.sub.ELI was determined from more than 5 independent clones on average.

DETDESC:

DETD(38)

FIG. 1 contains an analysis of **AIDS** virus isolates, showing:
DETDESC:

DETD(39)

A/ Restriction maps of the inserts of phage lambda clones derived from cells infected with **LAV**.sub.ELI (E-H12) and with **LAV**.sub.MAL (hereinfter "M-H11"). The schematic genetic organization of the **AIDS** virus has been drawn above the maps. The LTRs are indicated by solid boxes. Restriction sites are indicated as follows:. . .
DETDESC:

DETD(40)

B/ A comparison of the sites for seven restriction enzymes in six isolates: the prototype **AIDS** virus **LAV**.sub.BRU, **LAV**.sub.MAL and **LAV**.sub.ELI ; and Z1, Z2 and Z3. Restriction sites are represented by the following symbols vertically aligned with the symbols in. . .

DETDESC:

DETD(41)

FIG. 2 shows the genetic organization of the central region in **AIDS** virus isolates. Stop codons in each phase are represented as vertical bars. Vertical arrows indicate possible AUG initiation codons. Splice. . . (A) and donor (D) sites identified in subgenomic viral mRNA [Muesing et al., 1985] are shown below the graphic of **LAV**.sub.BRU; and corresponding sites in **LAV**.sub.ELI and **LAV**.sub.MAL are indicated. PPT indicates the repeat of the polypurine tract flanking the 3'LTR. As observed in **LAV**.sub.BRU [Wain-Hobson et al., 1985], the PPT is repeated 256 nucleotides 5' to the end of the pol gene in both the **LAV**.sub.ELI and **LAV**.sub.MAL sequences, but this repeat is degenerated at two positions in **LAV**.sub.ELI.

DETDESC:

DETD(42)

FIG. 3 shows an alignment of the protein sequences of four **AIDS** virus isolates. Isolate **LAV**.sub.BRU [Wain-Hobson et al., 1985] is taken as reference; only differences with **LAV**.sub.BRU are noted for ARV 2 [Sanchez-Pescador et al., 1985] and the two Zairian isolates **LAV**.sub.MAL and **LAV**.sub.ELI. A minimal number of gaps (-) were introduced in the alignments. The NH.sub.2 -termini of p25.sup.gag and p18.sup.gag are indicated. . .

DETDESC:

DETD(43)

FIG. . . . homologous proteins of different isolates. Part A of each table gives results deduced from two-by-two alignments using the proteins of **LAV**.sub.BRU as reference, part B, those of **LAV**.sub.ELI as reference. Sources: Muesing et al., 1985 for HTLV-3 ; Sanchez-Pescador et al., 1985 for ARV 2 and Wain-Hobson et al., 1985 for **LAV**.sub.BRU. For each case in the tables, the size in amino acids of the protein (calculated from the first methionine residue. . .

DETDESC:

DETD(44)

FIG. 5 shows the variability of the **AIDS** virus envelope protein. For each position x of the alignment of env (FIG. 3), variability V(x) was calculated as: V(x)=number. . .

DETDESC:

DETD(45)

FIG. 6 shows the direct repeats in the proteins of different **AIDS** virus isolates. These examples are derived from the aligned sequences of gag (a, b), F (c,d) and env (e, f,. . .

DETDESC:

DETD(46)

FIG. 7A-7I show the complete cDNA sequence of **LAV**.sub.ELI of this invention.

DETDESC:

DETD(47)

'The . . . a first amino acid of the open-reading frames concerned, although these numbers do not correspond exactly to those of the **LAV**.sub.ELI proteins concerned, rather to the corresponding proteins of the **LAV**.sub.BRU or sequences shown in FIGS. 3A, 3B and 3C. Thus a number corresponding to a "first amino acid residue" of a **LAV**.sub.ELI protein corresponds to the number of the first amino-acyl residue of the corresponding **LAV**.sub.BRU protein which, in any of FIGS. 3A, 3B or 3C, is in direct alignment with the corresponding first amino acid of the **LAV**.sub.ELI protein. Thus the sequences concerned can be read from FIGS. 7A-7I to the extent where they do not appear with. . .
DETDESC:

DETD(62)

Proteins . . . production of immunogenic compositions and (preferably in relation to the stretches of the env protein) of vaccine compositions against the **LAV**-1 viruses.

DETDESC:

DETD(63)

The . . . will be able to obtain them all, for instance by cleaving an entire DNA corresponding to the complete genome of **LAV**.sub.ELI, such as by cleavage by a partial or complete digestion thereof with a suitable restriction enzyme and by the subsequent. . .
DETDESC:

DETD(65)

b) DNA fragments corresponding to genes can be cloned into expression **vectors** for E. coli, yeast- or **mammalian** cells and the resultant proteins purified.

DETDESC:

DETD(66)

c) . . . generate fusion polypeptides. Recombinants, producing antigenically competent fusion proteins, can be identified by simply screening the recombinants with antibodies against **LAV** antigens.
DETDESC:

DETD(68)

More particularly the invention relates to such modified DNA recombinant **vectors** modified by the above-said DNA sequences

and which are capable of transforming higher eucaryotic cells particlularly, **mammalian** cells. Preferably, any of the above-said sequences are placed under the direct control of a promoter contained in said **vectors** and recognized by the polymerases of said cells, such that the first nucleotide codons expressed correspond to the first triplets. . . DNA sequences. Accordingly, this invention also relates to the corresponding DNA fragments which can be obtained from the genome of **LAV**.sub.ELI or its cDNA by any appropriate method. For instance, such a method comprises cleaving said **LAV**.sub.ELI genome or its cDNA by restriction enzymes preferably at the level of restriction sites surrounding said fragments and close to. . . permit the reconstitution of the nucleotide extremities of said fragments. Those fragments may then be inserted in any of said **vectors** for causing the expression of the corresponding polypeptide by the cell transformed therewith. The corresponding polypeptide can then be recovered. . .

DETDESC:

DETD(69)

The . . . carrying said fragments. Using the cloned DNA fragments as a molecular hybridization probe--either by labelling with
radionucleotides or with fluorescent reagents--**LAV** virion RNA may be detected directly in the blood, body fluids and blood products (e.g. of the antihemophylic factors such. . . vaccines (e.g., hepatitis B vaccine). It has already been shown that whole virus can be detected in culture supernatants of **LAV** producing cells. A suitable method for achieving that detection comprises immobilizing virus on a support (e.g., a nitrocellulose filter), disrupting. . .

DETDESC:

DETD(70)

Probes . . . to the invention can also be used for rapid screening of genomic DNA derived from the tissue of patients with **LAV** related symptoms, to see if the proviral DNA or RNA present in host tissue and other tissues can be related to that of **LAV**.sub.ELI.

DETDESC:

DETD(71)

A . . . of said DNA, electrophoresis of the fragments and Southern blotting of genomic DNA from tissues, subsequent

hybridization with labelled cloned **LAV** proviral DNA. Hybridization in situ can also be used.

DETDESC:

DETD(73)

The DNAs or DNA fragments according to the invention can be used also for achieving the expression of viral antigens of **LAV**.sub.ELI for diagnostic purposes.

DETDESC:

DETD(75)

More . . . having the same polypeptidic backbone as the polypeptides mentioned hereinabove) bearing an epitope characteristic of a protein or glycoprotein of **LAV**.sub.ELI, which polypeptide or molecule then has N-terminal and C-terminal extremities respectively either free or, independently from each other, covalently bonded. . . to amino acids other than those which are normally associated with them in the larger polypeptides or glycoproteins of the **LAV** virus, which last mentioned amino acids are then free or belong to another polypeptidic sequence. Particularly, the invention relates to. . . any of the epitope-bearing-polypeptides which have been defined more specifically hereinabove, recombined with other polypeptides fragments normally foreign to the **LAV** proteins, having sizes sufficient to provide for an increased immunogenicity of the epitope-bearing-polypeptide yet, said foreign polypeptide fragments either being. . .

DETDESC:

DETD(83)

The . . . obtained by methods, such as are disclosed in the earlier patent applications referred to above, in a purified state from **LAV**.sub.ELI virus preparations or--as concerns more particularly the peptides--by chemical synthesis, are useful in processes for the detection of the presence of anti-**LAV** antibodies in biological media, particularly biological fluids such as sera from man or animal, particularly with a view of possibly diagnosing LAS or **AIDS**.
DETDESC:

DETD(84)

Particularly . . . process of diagnosis making use of an envelope glycoprotein or of a polypeptide bearing an epitope of

this glycoprotein of **LAV**.sub.ELI for the detection of anti-**LAV** antibodies in the serums of persons who carry them. Other polypeptides--particular those carrying an epitope of a core protein--can be. . .

DETDESC:

DETD(91)

detecting the antigen-antibody-complex formed, which is then indicative of the presence of **LAV** antibodies in the biological fluid.
DETDESC:

DETD(94)

The invention also relates to the diagnostic kits themselves for the in vitro detection of antibodies against the **LAV** virus, which kits comprise any of the polypeptides identified herein and all the biological and chemical reagents, as well as. . .

DETDESC:

DETD(95)

It can of course be of advantage to use several proteins or polypeptides not only of **LAV**.sub.ELI, but also of **LAV**.sub.MAL together with homologous proteins or polypeptides of earlier described viruses, such as **LAV**.sub.BRU, HTLV-3, ARV 2, etc.

DETDESC:

DETD(96)

The . . . vaccine compositions whose active principle is to be constituted by any of the antigens, i.e., the hereinabove disclosed polypeptides of **LAV**.sub.ELI, particularly the purified gp110 or immunogenic fragments thereof, fusion polypeptides or oligopeptides in association with a suitable pharmaceutically or physiologically. . . units, preferably less than 150, particularly from 5 to 150 amino acid residues, as deducible for the complete genome of **LAV**.sub.ELI and even more preferably those peptides which contain one or more groups selected from Asn-X-Thr and Asn-X-Ser as defined above.. . .

DETDESC:

DETD(97)

The . . . identification and even determination of relative proportions of the different polypeptides or proteins in biological samples, particularly human samples containing **LAV** or related viruses.

DETDESC:

DETD(99)

Finally . . . for transforming eucaryotic cells of human origin, particularly lymphocytes, the polymerase of which are capable of recognizing the LTRs of **LAV**. Particularly said vectors are characterized by the presence of a **LAV** LTR therein, said LTR being then active as a promoter enabling the efficient transcription and translation in a suitable host. . . .

DETDESC:

DETD(100)

Needless . . . fragments (ORFs) having substantially equivalent properties, all of said genomes belonging to retroviruses which can be considered as equivalents of **LAV**.sub.ELI. It must be understood that the claims which follow are also intended to cover all equivalents of the products (glycoproteins,. . .

DETDESC:

DETD(102)

It . . . preferably one or more of the polypeptides, which are specifically identified above and which have the amino acid sequences of **LAV**.sub.ELI that have been identified, or peptide sequences corresponding to previously defined **LAV** proteins. In this respect, the invention relates more particularly to the particular polypeptides which have the sequences corresponding more specifically to the **LAV**.sub.BRU sequences which have been referred to earlier, i.e., the sequences extending between the following first and last amino acids, of the **LAV**.sub.BRU proteins themselves, i.e., the polypeptides having sequences contained in the **LAV**.sub.BRU OMP or **LAV**.sub.BRU TMP or sequences extending over both, particularly those extending from between the following positions of the amino acids included in the env open reading frame of the **LAV**.sub.BRU genome,

DETDESC:

DETD(113)

Phage .lambda. clone E-H12 derived from **LAV**.sub.ELI infected cells has been deposited at the CNCM under No. I-550 on May 9, 1986. Phage clone M-H11 derived from **LAV**.sub.MAL infected cells has been deposited at the CNCM under No. I-551 on May 9, 1986.

DETDESC:

DETD(116)

Allan, . . . Rosen, C. A., Haseltine, W. A., Lee, T. H., & Essex, M. (1985a). Major glycoprotein antigens that induce antibodies in **AIDS** patients. Science 228, 1091-1094.

DETDESC:

DETD(117)

Allan, . . . J. E., Lee, T. H., McLane, M. F., Kanki, P. J., Groopman, J. E., & Essex, M. (1985b). A new **HTLV**-**III**/**LAV** antigen detected by antibodies from **AIDS** patients. Science 230, 810-813.

DETDESC:

DETD(118)

Arya, S. K., Guo, C., Josephs, S. F., & Wong-Staal, F. (1985). Trans-activator gene of human T-lymphotropic virus type III (**HTLV**-**III**). Science 229, 69-73.

DETDESC:

DETD(119)

Bailey, A. C., Downing, R. G., Cheinsong-Popov, R., Tedder, R. C., Dalgleish, A. G., & Weiss, R. A. (1985). **HTLV**-**III** serology distinguishes atypical and endemic Kaposi's sarcoma in Africa. Lancet I, 359-361.

DETDESC:

DETD(121)

Barre-Sinoussi, . . . W. & Montagnier, L. (1983). Isolation of a T-lymphotropic retrovirus from a patient at risk of acquired immune deficiency syndrome (**AIDS**). Science 220, 868-870.

DETDESC:

DETD(122)

Been, . . . T., Gold, J., Baker, L. McCormick, J. Feorino, P., Piot, P., Quinn T. & Martin, M. (1985). Genomic heterogeneity of **AIDS** retroviral isolates from North America and Zaire. Science 230, 949-951.
DETDESC:

DETD(124)

Brun-Vesinet, . . . C., Desmyter, J., Feinsod, F., & Quinn T. C. (1984). Prevelance of antibodies to lymphadenopathy-associated virus in African patients with **AIDS**. Science 226, 453-456.

DETDESC:

DETD(125)

Chang, . . . C. W., Huang, J. & Chang, T. W. (1985). Expression in Escheridia coli of open reading frame gene segments of **HTLV**-**III**. Science 228, 93-96.

DETDESC:

DETD(127)

Nucleotide sequence evicence for relationship of **AIDS** retrovirus to lentiviruses. Nature 317, 366-368. Clark, S. P., & Mak, T. W., (1984). Fluidity of a retrovirus genome. J.. . .

DETDESC:

DETD(128)

Clavel, F., Klatzmann, D., & Montagnier, L., (1985). Deficient neutralizing capacity of sera from patients with **AIDS** or related syndromes. Lancet I, 879-880.

DETDESC:

DETD(129)

Clavel, . . . C., Rey, F., Champelinaud, J. L., Nina, J, S., Mansinho, K., Santos-Ferreira, M. O., Klatzmann, D., & Montagnier, L. (1986). **LAV** type II: a second retrovirus associated with **AIDS** in West-Africa. C. R. Acad. Sci. Paris 302, 485-488.

DETDESC:

DETD(132)

Dalgleish, . . . M. F. & Weiss, R. A. (1984). The CD4 (T4) antigen is an essential component of the receptor for the **AIDS** retrovirus. Nature 312, 763-767.

DETDESC:

DETD(135)

DiMarzoVeronese, . . . S., Gallo, R. C., & Sarngadharan, M. G. (1985). Characterization of gp 41 as the transmembrane protein coded by the **HTLV**-**III**/**LAV** envelope gene. Science 229, 1403-1405.
DETDESC:

DETD(137)

Isolation of human T-lymphotropic retrovirus (**LAV**) from Zairan married couple, one with **AIDS**, one with prodromes. Lancet I, 1383-1385.

DETDESC:

DETD(138)

Hahn, . . . G. M., Arya, S. U., Popovic, M., Gallo, R. C., & Wong-Staal, F. (1984). Molecular cloning and characterization of the **HTLV**-**III** virus associated with **AIDS**. Nature 312, 166-169.
DETDESC:

DETD(140)

Kan, . . . Franchini, G., Wong-Staal, F., Dubois, G. C., Robey, W. G., Lautenberger, J. A., & Papas, T. S. (1986). Identification of **HTLV**-**III**/**LAV** sor gene product and detection of antibodies in human sera. Science 231, 1553-1555.

DETDESC:

DETD(143)

Klatzmann, . . . D., Hercend, T., Gluckman, J .C., & Montagnier, L. (1984). T-lymphocyte T4 molecule behave as the receptor for human retrovirus **LAV**. Nature 312, 767-768.

DETDESC:

DETD(146)

Lee, T. H., Coligan, J. E. Allan, J. S., McLane, M. F., Groopman, J. E. & Essex, M. (1986). A new **HTLV** **III**/**LAV** protein encoded by a gene found in cytopathic retroviruses. Science 231, 1546-1549.
DETDESC:

DETD(149)

MacDougal, . . . S., Kennedy, M. S., Sligh, J. M., Cort, S. P., Mawle, A. & Nicholson, J. K. A. (1986). Binding of **HTLV**-**III**/**LAV** to T4.sup.+ cells by a complex of the 110 k viral protein and the T4 molecule. Science 231, 382-385.
Messing,. . .
DETDESC:

DETD(153)

Muesing, . . . D., Benton, C. V., Lasky, L. A. & Capon, D. J. (1985). Nucleic acid structure and expression of the human **AIDS**/lymphadenopathy retroviruses. Nature 313, 450-458.
DETDESC:

DETD(154)

Norman, C. (1985). Politics and science clash on African **AIDS**. Science 230, 1140-1142. Piot, P., Quinn, T. C., Taelman, H., Feinsod, F. M., Minlangu, K. B., Wobin, O., Mbendi, N.,. . .

DETDESC:

DETD(156)

Rabson, A. B. & Martin, M. A. (1985). Molecular organization of the **AIDS** retrovirus. Cell 40, 477-480.

DETDESC:

DETD(157)

Ratner, . . . Papas, T. S., Ghrayeb, J., Chang, N. T., Gallo, R. C. & Wong-Staal, F. (1985). Complete nucleotide sequence of the **AIDS** virus, **HTLV**-**III**. Nature 313, 277-284.

DETDESC:

DETD(158)

Robinson, . . . & Haseltine, W. A. (1985). The location of

cisacting regulatory sequences in the human T cell lymphotropic virus type III (**HTLV**-**III**/**LAV**) long terminal repeat. Cell 41, 813-823.
DETDESC:

DETD(159)

Sanchez-Pescador, . . . Bernard, A., Randolph, A., Levy, J. A., Dina, D. & Luciw, P. A., (1985). Nucleotide sequence and expression of an **AIDS**-associated retrovirus (ARV-2). Science 227, 484-492.
DETDESC:

DETD(164)

Sonigo, . . . O., Retzel, E., Tiollais, P., Haase, A. & Wain-Hobson, S. (1985). Nucleotide sequence of the visna lentivirus: Relationship to the **AIDS** virus. Cell 42, 369-382.

DETDESC:

DETD(170)

Wain-Hobson, S., Sonigo, P., Danos, O., Cole, S., & Alizon, M. (1985). Nucleotide sequence of the **AIDS** virus, **LAV**. Cell 40, 9-17.
DETDESC:

DETD(173)

Weiss, . . . A., Weller, I. A. D. & Tedder, R. C. (1985). Neutralization of human T-lymphotropic virus type III by sera of **AIDS** and **AIDS**-risk patients, Nature, 316, 69-72.

CLAIMS:

CLMS(1)

We . . .
amino-acyl residues 490-620, amino-acyl residues 680-700, amino-acyl residues 1-530, amino-acyl residues 34-530, amino-acyl residues 531-877 of an envelope glycoprotein of **LAV**.sub.ELI virus.

CLAIMS:

CLMS(7)

7. . . . and Y is tyrosine,
and wherein said fragment comprises a p25 peptide comprising

amino-acyl residues 138-385 of gag protein of **LAV**.sub.ELI virus.
CLAIMS:

CLMS(8)

8. . . . and Y is tyrosine,
and wherein said fragment comprises a p13 peptide comprising amino-acyl residues 385-519 of gag protein of **LAV**.sub.ELI virus.
=> log y

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